New Methods for the Synthesis of Nitrogen Containing, Biologically Relevant Small Molecules

UNIVERSITY OF TASMANIA

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A thesis submitted in fulfilment of the requirements

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School of Physical Sciences (Chemistry)

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Abstract

The following thesis consists of two independent parts, both linked by a common theme of developing new methods for the synthesis of small nitrogen containing molecules. The first part is titled the oxidative dearomatisation of pyrrole, while the second part is titled the strain driven rearrangement of cyclopropenyl trichloroacetimidates.

The oxidation of pyrrole typically leads to uncontrolled polymerisation and decomposition, however it was postulated that under appropriate reaction conditions the controlled oxidation of pyrrole to 2-pyrrolinone would be possible. Thus, the controlled oxidation of electron rich pyrroles was achieved in good to excellent yields with the hypervalent iodine oxidant Dess−Martin periodinane, and also its synthetic precursor 2-iodoxybenzoic acid (IBX). The sensitized photo-oxidation of pyrrole was also examined by utilizing the narrow spectrum light emission from LEDs. This led to an optimised method for the photo-oxidation of a range of pyrroles to produce 2-pyrrolinones in good to high yields; a result that was only possible due to limiting the absorbance of light by pyrrole and selectively exciting the dye sensitizer for the oxidation. The products from the methods of controlled pyrrole oxidation have been used in an initial study towards the total synthesis of pyrrolidine alkaloid natural products including preussin, codonopsinine and crispine A.

Nitrogen-substituted benzylidene cyclopropanes were prepared by a strain-driven Overman rearrangement of cyclopropenyl trichloroacetimidates in good to excellent yields. This methodology demonstrates the first rearrangement of a cyclopropene to an alkylidenecyclopropane with a nitrogen atom participant. The product benzylidene cyclopropanes were used as precursors to biologically relevant cyclopropyl ureas and saturated cyclopropanes.

Abbreviation list

AcOH	Acetic Acid
dppe	1,2-Bis(diphenylphosphino)ethane
9-BBN	9-Borabicyclo[3.3.1]nonane
Bop	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Bn	Benzyl
DPE-Phos	Bis(2-diphenylphosphinophenyl) ether
TBS	*tert*-Butyldimethylsilyl ether
Bu	Butyl
CDI	1,1'-Carbonyldiimidazole
cod	1,5-Cyclooctadiene
CSA	Camphorsulfonic acid
Cbz	Carboxybenzyl
*m*CPBA	*meta*-Chloroperoxybenzoic acid
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-Dimethylaminopyridine
°C	Degrees Celsius
C	Carbon
Boc	Di-*tert*-butyl dicarbonate
DIBAL-H	Diisobutylaluminium hydride
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
EtOH	Ethanol
Et	Ethyl
HFIP	Hexafluoroisopropanol
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
h	Hour(s)
HIV	Human immunodeficiency virus
H	Hydrogen
IBX	2-Iodoxybenzoic acid

IR	Infrared
*i*PrOH	Isopropanol
LG	Leaving Group
hv	Light
LED	Light Emitting Diode
LDA	Lithium diisopropylamide
Ms	Methanesulfonyl
Me	Methyl
min(s)	Minute(s)
MS	Molecular Sieves; Mass Spectrometry
Ns	4-Nitrobenzenesulfonyl
Nu	Nucleophile
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
NOSEY	Nuclear Overhauser effect spectroscopy
ppm	Parts Per Million
PIFA	Phenyliodine bis(trifluoroacetate)
PIDA	Phenyliodine diacetate
Py	Pyridine
PCC	pyridinium chlorochromate
rt	Room Temperature
SE	Strain Energy
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TMP	Tetramethylpiperidine
TPP	Tetraphenylporphyrin
TLC	Thin-layer chromatography
TsOH	*para*-Toluenesulfonic acid
Ts	*para*-Toluenesulfonyl
TBD	Triazabicyclodecene
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

OTf	Trifluoromethanesulfonate
TMS	Trimethylsilyl
UV	Ultraviolet
W	Watts

Publications

Howard, J. K.; Hyland, C. J. T.; Just, J.; Smith, J. A. Controlled Oxidation of Pyrroles: Synthesis of Highly Functionalized γ-Lactams. *Org. Lett.* **2013**, *15*, 1714–1717.

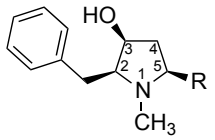
Howard, J. K.; Amin, C.; Lainhart, B.; Smith, J. A.; Rimington, J.; Hyland, C. J. T. Synthesis of Nitrogen-Substituted Methylenecyclopropanes by Strain-Driven Overman Rearrangement of Cyclopropenylmethyl Trichloroacetimidates. *J. Org. Chem.* **2014**, *79*, 8462–8468.

Part 1: The Oxidative Dearomatisation of Pyrrole

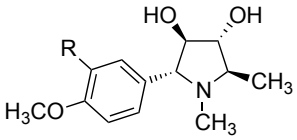
Chapter 1 – Introduction

1.1 Pyrrolidine natural products and synthetic strategies

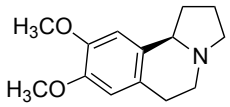
Cyclic, nitrogen containing molecules are interesting small molecules to study due to their wide range of biological and material properties,[1,2] as well as their deceptive structural simplicity.[3] Pyrrolidine alkaloids are a class of saturated nitrogen containing heterocycles that posses a single nitrogen atom with four carbon atoms. This class of compounds has been widely studied synthetically due to their biological activities.[4] The alkaloids are structurally diverse in nature, and while synthetic methods have improved and the field of synthetic organic chemistry has matured, targeting these compounds remains a significant challenge for the synthetic chemist.



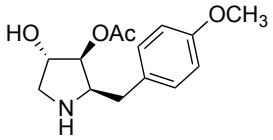
Preussin R = C_9H_{19} (**1**)
Preussin B R = C_7H_{17} (**2**)



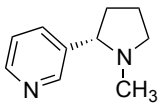
Codonopsinine R=H (**3**)
Codonopsine R=OCH_3 (**4**)



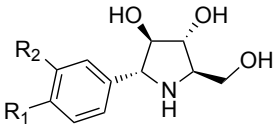
Crispine A (**5**)



Anisomycin (**6**)



Nicotine (**7**)



Radicamine A R_1=OCH_3, R_2=OH (**8**)
Radicamine B R_1=OH, R_2=H (**9**)

Figure 1: *A variety of naturally occurring pyrrolidine alkaloids illustrating their structural diversity.*

In nature pyrrolidine alkaloids are found in numerous environments, yet as is the case with many natural products, are typically only present in small amounts. For example, codonopsinine (**3**) and its analogue codonopsine (**4**) were first isolated in 1969 by Matkhalikova and co-authors, from the herbaceous plant *Codonopsis clematidea* with further structural assignment and corrections coming in 1972 with the use of NMR spectroscopy.[5-7] Matkhalikova and co-workers report that the plant contains only 0.04−0.08 wt/wt of total alkaloid material, with a smaller fraction of that mixture being made up of codonopsinine (**3**) and codonopsine (**4**). These compounds have been shown to display antibiotic activities as well as hypotensive activities.[8] To date there have been fifteen separate accounts describing the total synthesis of codonopsinine (**3**) and/or codonopsine (**4**).

Another example of a pyrrolidine alkaloid of significant interest is preussin (**1**), which was first isolated in 1988 from the fungus *Aspergillus ocheceus* by Schwartz and co-workers.[9] It was later observed to be produced within the fermented broths of *Preussia sp*. in 1989 by Johnson and co-workers.[10] As with codonopsinine (**3**), preussin (**1**) exhibits a wide range of biological properties including antifungal activity against filamentous fungi and yeasts,[11] antiviral activities,[12] as well as inducing apoptosis, or cell death, in human cancer cells.[13] Recently, Fukuda and colleagues have isolated preussin (**1**) and identified preussin B (**2**) from the pathogenic fungi *Simplicillium lanosoniveum*, which reportedly displays antifungal activity against *Saccharomyces cerevisiae*, suggesting that the metabolites are produced as part of a defense mechanism.[14] Furthermore, Fukuda and co-workers have conducted the first ^{13}C labelling study for the biosynthesis of these alkaloids, with the conclusion that the parent fungus enzymatically uses malonate and phenylalanine (**10**) to construct the functionalised ring *via* an intermolecular cyclisation as a result of either reductive amination, or through Dieckman condensation (Figure 2).

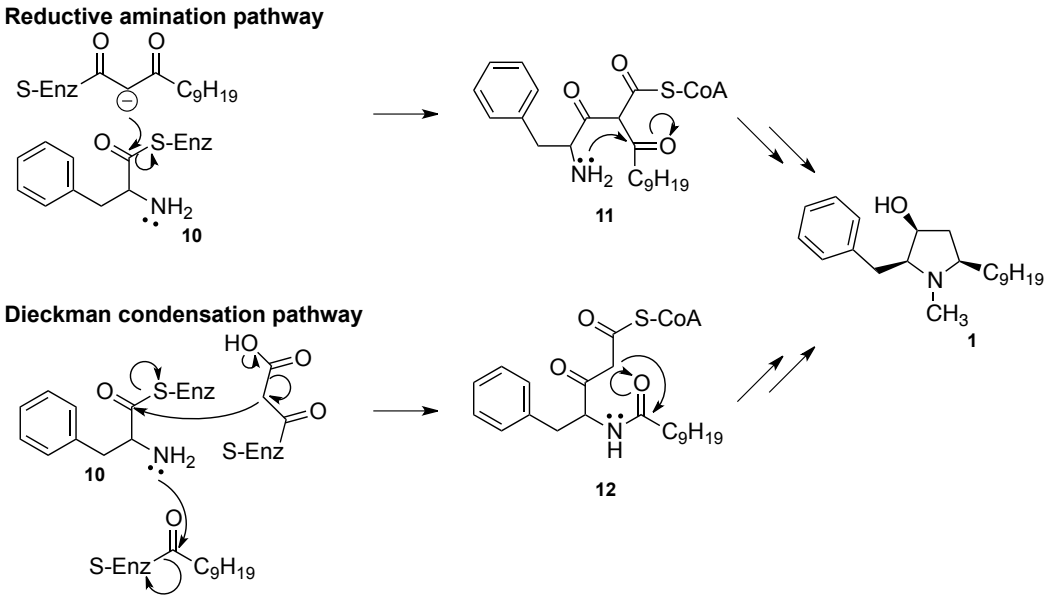
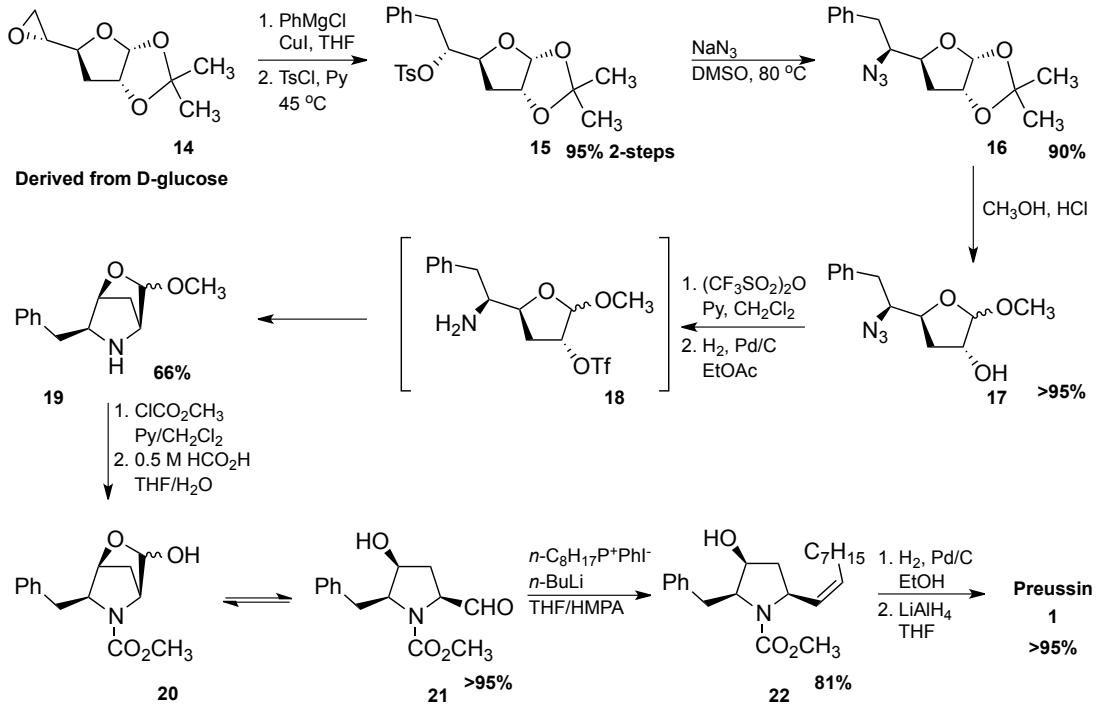


Figure 2: *Fukuda's two proposed biosynthesis pathways of preussin*[14]

The synthesis of pyrrolidine alkaloids has been approached through many different strategies. As an example of some of the strategies used to synthesise these alkaloids, the following discussion will focus on a wide selection of syntheses for targeting preussin (**1**), which will provide a representation of present literature methods. To date there have been over thirty reported racemic or asymmetric total syntheses of

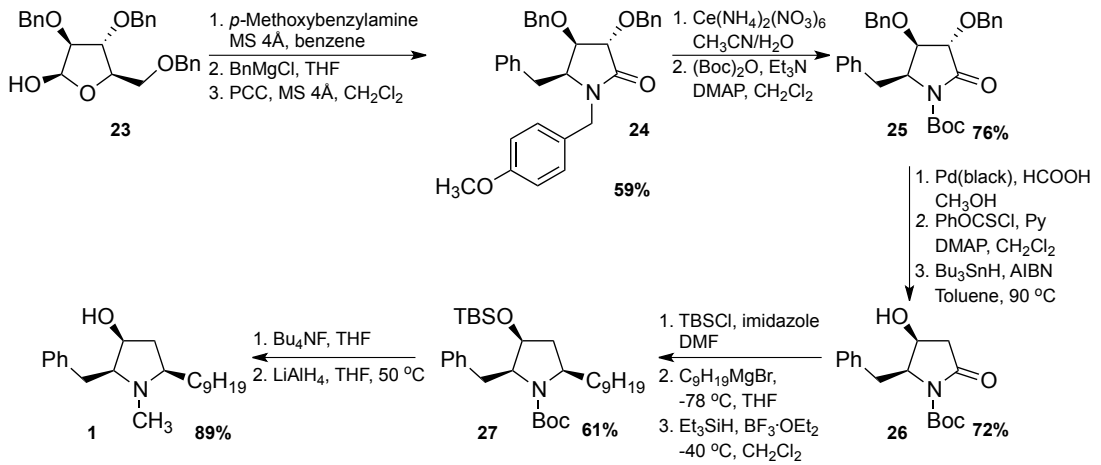
preussin (**1**). It should also be noted that while many methods are quite elegant and high-yielding, chiral-pool precursors are commonly employed to template pre-defined stereochemistry to preussin (**1**).

The first total synthesis of preussin (**1**) was by Pak and Lee in 1991, three years after the alkaloids initial isolation, using D-glucose (**13**) as the starting material (Scheme 1).[15] The use of D-glucose (**13**) as a starting point is convenient as the stereogenic centres at the C2, C3 and C5 positions of the sugar unit can be transferred to the C2, C3 and C5 positions of preussin. As such, D-glucose underwent protection and deoxygenation to furanose **14** through a method developed by Barton and McCombie.[16] The epoxide of furanose **14** was treated with phenylmagnesium chloride and cuprous iodide to install the phenyl functionality of preussin, which was followed by the S_N2 substitution of tosylate **15** to give azide **16**. The acetonide protecting group was removed with methanolic HCl to generate the β-anomer **17a** (84% yield) and the α-anomer **17b** (16% yield). Both isomers were treated with triflic anhydride before reduction of the azide to the analogous primary amine **18**, which then served as the nucleophile in a nucleophilic substitution to generate the pyrrolidine ring system of **19**. The amine was protected as the carbamate before hydrolysis of the acetal group to produce the equilibration mixture of lactol **20** and aldehyde **21**. This mixture was treated under Wittig conditions to install the alkenyl side chain followed by subsequent reductions of both the alkene and the carbamate to generate (+)-preussin (**1**).



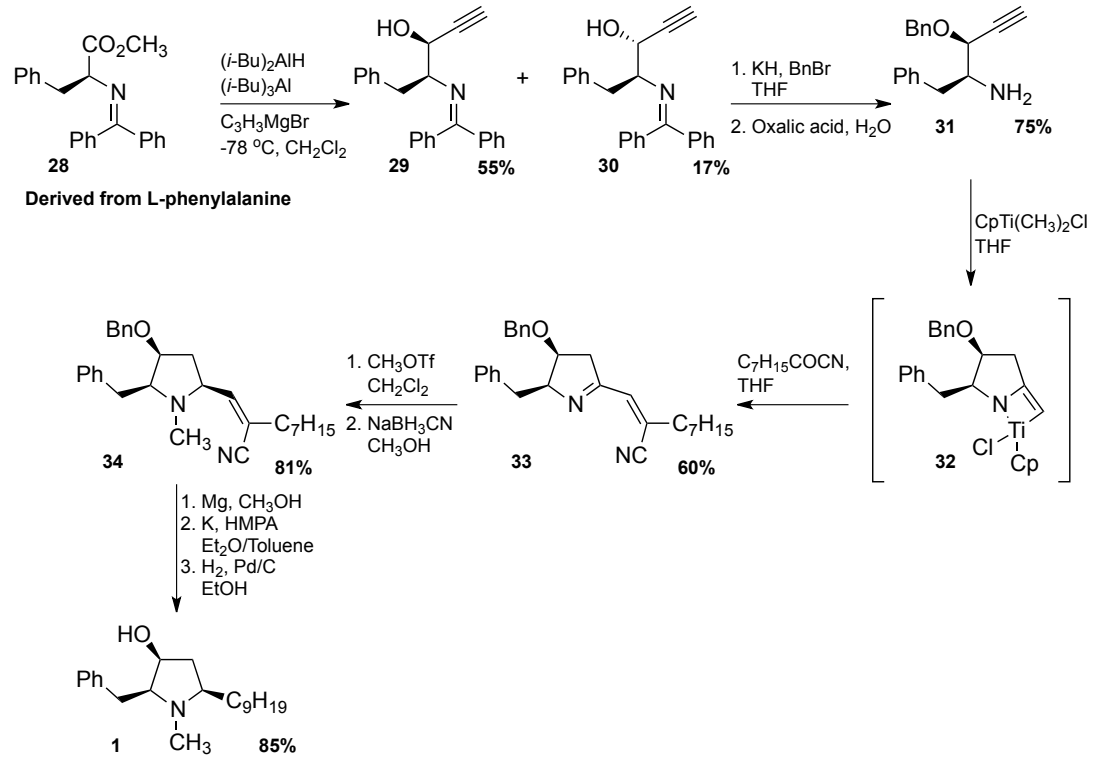
Scheme 1: *Pak and co-workers synthesis of preussin from furanose* ***14***

A modified furanose strategy towards preussin was employed by Yoda and co-workers in which they manipulated commercially available 2,3,5-tri-O-benzyl-β-D-arabinofuranose (**23**) to the highly functionalised enantiomerically pure *N*-*p*-methoxybenzyl lactam **24** (Scheme 2).[17] A series of deprotection/protection steps took place on lactam **24** before a radical mediated regioselective deoxygenation at the C3 position of the ring of lactam **25**. A Grignard reaction followed by reduction of the amide carbonyl of **26** installed the alkyl chain at the C2 position of the ring. Finally, a global reduction revealed preussin (**1**).



Scheme 2: *Yoda and co-workers synthesis of preussin from furanose*

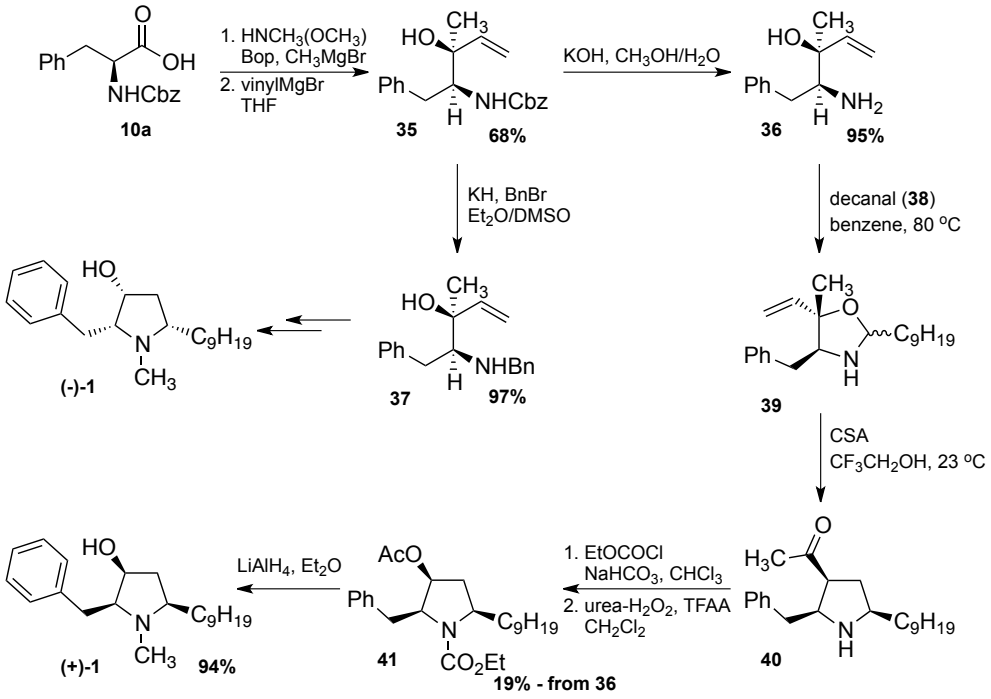
In a similar fashion to using sugar based materials as starting points for the templated synthesis of preussin, there have been many strategies that have taken advantage of the inherent stereochemistry available in amino acids, primarily L-phenylalanine (**10**). In 1993, McGrane and Livinghouse were the first to adopt an L-phenylalanine (**10**) derived material as their starting point for the synthesis of preussin (**1**) (Scheme 3). Following the construction of methyl *N*-(diphenylmethylene)-L-phenylalaninate (**28**), a modified Grignard reaction took place where a 1:1 mixture of DIBAL-H and $(i\text{-Bu})_3Al$ was used to reduce the methyl ester of **28** to an aldehyde in the presence of propargylmagnesium bromide to generate a separable 3.2:1 mixture of the *cis*-alcohol **29** and the *trans*-alcohol **30**. After benzyl protection of the alcohol, hydrolysis with oxalic acid was preformed to generate the free amine **31**, which in the presence of a suitable titanium catalyst underwent imidotitanium-alkyne [2+2] cycloaddition to generate cyclic imine **33**, after quenching with octanoyl cyanide. This cyclic species was *N*-methylated followed by a series of reductive steps to reveal preussin (**1**).



Scheme 3: *McGrane and Livinghouse's preussin synthesis from a L-phenylalanine derivative*

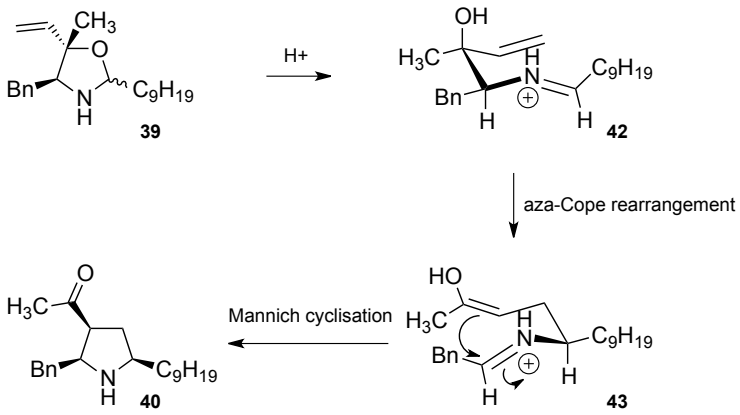
Deng and Overman also used L-phenylalanine (**10**) as their starting material in the synthesis of both enantiomers of preussin (Scheme 4).[18] The focus of their synthesis was a selective aza-Cope−Mannich rearrangement, which was controlled by the

substituent on the nitrogen. From the *N*-Cbz protected L-phenylalanine **10a**, the desired amino alcohol intermediate **35** was constructed *via* Weinreb amide-mediated Grignard methylation of the acid, followed by a Grignard reaction to insert the allyl group. This intermediate underwent deprotection to yield either primary amine **36** or a deprotection/reprotection sequence to secondary amine **37**, with the former leading to natural preussin (+)-**1** and the later leading to the enantiomer (−)-**1**.



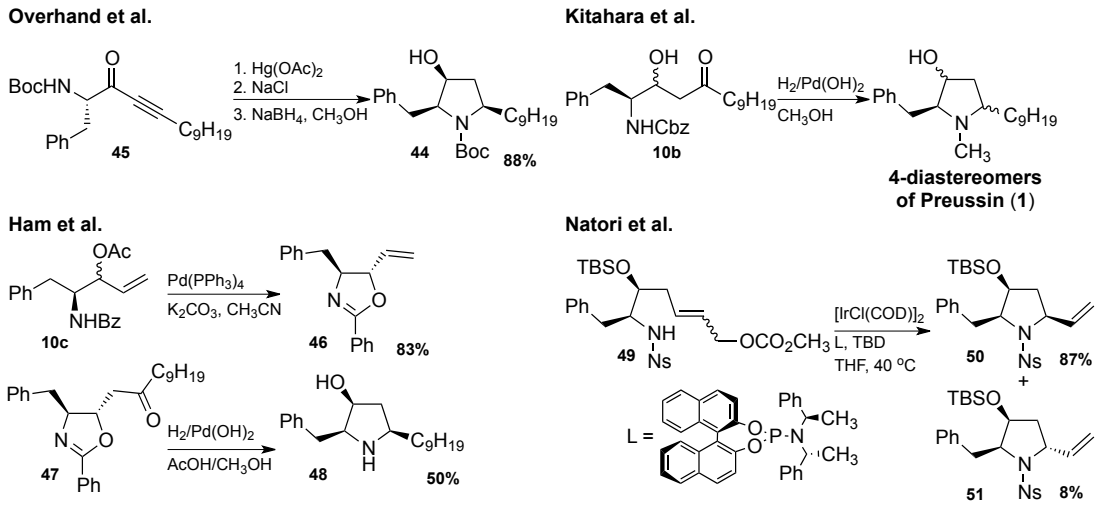
Scheme 4: *Deng and Overman's synthesis of preussin from L-phenylalanine*

To synthesise preussin, primary amine **36** was condensed with *n*-decanal (**38**) to give the oxazolidine **39**. This species underwent the proposed aza-Cope−Mannich rearrangement with camphorsulfonic acid to give the desired all-*cis* pyrrolidine **40** as the major product (Scheme 5). The stereochemical outcome was explained from the two intermediate stereoisomeric iminium ions that were in equilibrium as a result of acid mediated ring opening of the oxazolidine **39**, with the *E*-isomer being favoured with primary amines. This pyrrolidine underwent a short series of manipulations to produce natural preussin (+)-(**1**).



Scheme 5: *The aza-Cope−Mannich rearrangement as demonstrated by Deng and Overman*

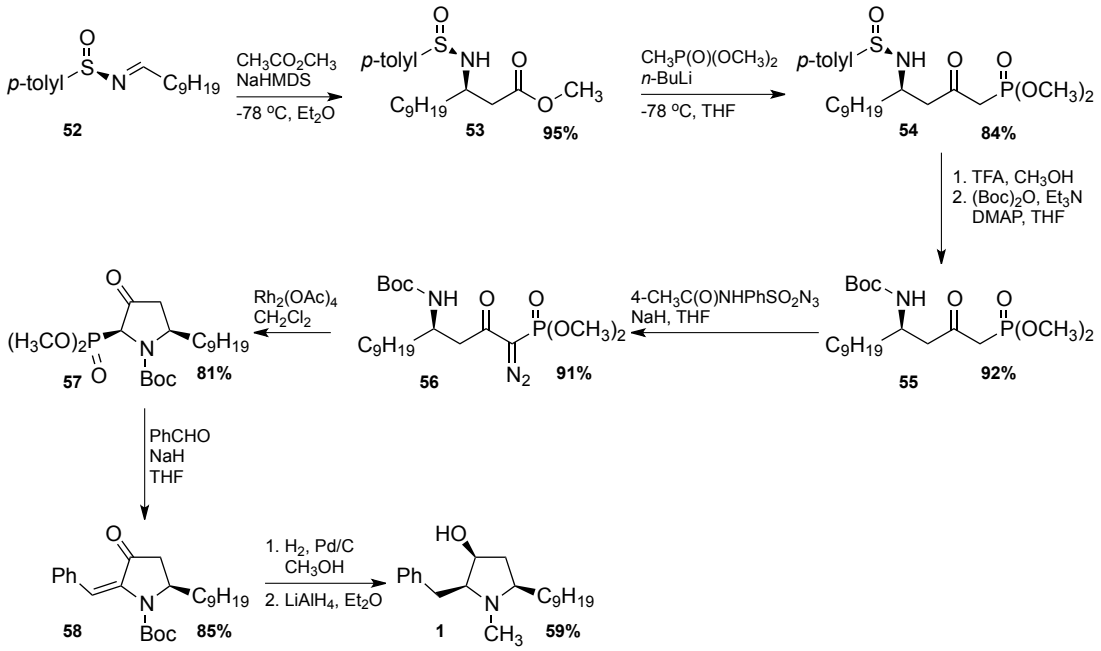
Other notable preussin syntheses using L-phenylalanine (**10**) derivatives as starting materials include (Scheme 6); Overhand and Hecht's short synthesis, which focuses on forming pyrrolidine **44** through a Hg(II) ring closure with ynone **45**,[19] Kitahara and co-workers synthesis that constructed a mixture of all stereoisomers of preussin from L-phenylalaninal derived ketone **10b**,[20] Ham and co-workers synthesis focusing on the construction of an intermediate oxazoline **46** through Pd(0) catalysed conditions from acetoxyl-L-phenylalanine **10c** before generation of the desired pyrrolidine with Pearlman's catalyst,[21] and most recently, Natori and Takahata's synthesis taking advantage of the intermolecular iridium-catalysed amination to generate the desired cyclic pyrrolidine **50**.[22]



Scheme 6: *A series of notable L-phenylalanine derived syntheses towards preussin*

There were many synthetic strategies involving the installation of stereochemistry on linear molecules before a ring-closing step was achieved, and two notable examples for the syntheses of preussin (**1**) standout in this category. The first of which was

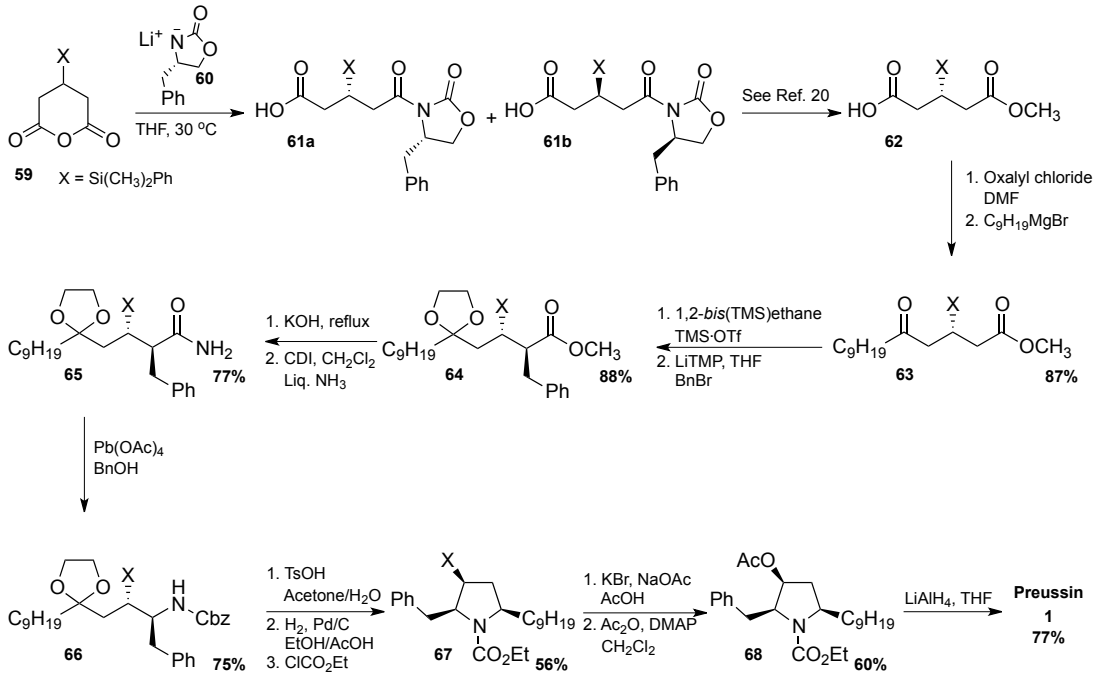
from Davis and co-workers who initially constructed the pyrrolidine core from a chiral sulfinamide and an unsaturated aldehyde in 2004.[23,24] However, after evaluating their own synthesis, they synthesised preussin more efficiently in 2008 (Scheme 7).[25] Starting from a chiral sulfinamide and unsaturated aldehyde they constructed sulfinimine **52**. The sulfinimine **52** was treated with the sodium enolate of methyl acetate to produce sulfinamide **53** before producing phosphonate **54** after attack with the carbanion of dimethyl methylphosphonate. The sulfur protecting group of **54** was exchanged for Boc-protection of the amine before phosphonate **55** was treated with 4-carboxybenzenesulfonylazide to generate the diazo intermediated **56**. Compound **56** was cyclised to produce the 3-oxopyrrolidine-2-phosphonate **57** *via* a Rh carbenoid, which upon Wadsworth−Horner−Emmons reaction with benzaldehyde produced enone **58**. The enone then underwent a series of reduction steps to produce preussin (**1**).



Scheme 7: *Davis and co-workers sulfinamide based synthesis of preussin from 2008*

The second notable example came from Ghosh, Verma and Chowdhury.[26-28] The synthesis of preussin was achieved from the *meso*-anhydride **59**, which was opened by the lithium anion of Evans' chiral auxiliary (**60**) (Scheme 8). This produced a 67:33 mixture of diastereoisomeric carboxylic acids that were readily separated by flash column chromatography with the major acid **61a** initially being taken through to preussin. However, later modifications of the synthesis allowed for both carboxylic acids **61a** and **61b** to be manipulated to the common carboxylic acid **62**,

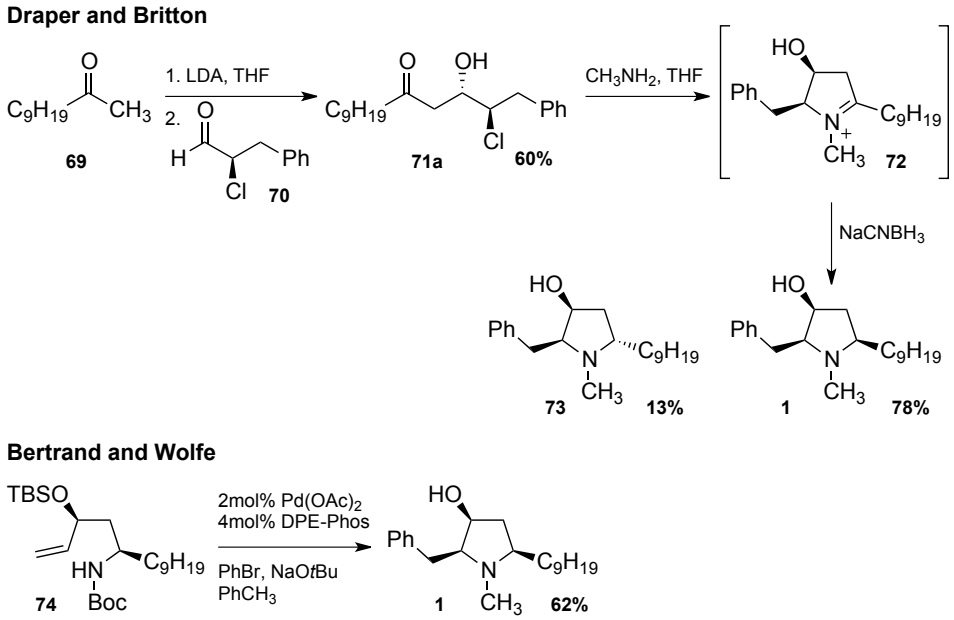
which was subsequently used in the revised preussin synthesis.[27] Acid **62** was treated with oxalyl chloride to generate the acid chloride derivative before a Grignard reaction with nonylmagnesium bromide to produce keto ester **63**, which was subsequently protected as the acetal **64**. The benzyl group was installed α to the carbonyl of the methyl ester before conversion to primary amide **65.** The resulting amide underwent a modified Curtius rearrangement with $Pb(OAc)_4$ to afford secondary amide **66**. After the acetal and Cbz-group removal the free amine reacted with the carbon of the carbonyl in a reductive amination to give the pyrrolidine **67**. Through a series of functional group manipulations, including a Fleming−Tamao oxidation to exchange silicon for oxygen, they were able to generate preussin (**1**).



Scheme 8: *The modified synthesis of preussin from Ghosh and co-workers in 1999*

Another method for constructing preussin that was of significant interest was Draper and Britton's three step synthesis of preussin in an overall 42% yield (Scheme 9).[29] This synthesis featured the reaction of the lithium enolate of 2-undecanone (**69**) with the enantiomerically pure (*R*)-2-chloro-3-phenylpropanal (**70**) to produce a 4:1 ratio of diastereomeric chlorohydrins **71** that were easily purified by crystallisation. Chlorohydrin **71a** was reacted with methylamine to generate the intermediate cyclic iminium ion **72** that was reduced *in situ* to yield preussin. The C5 epimer **73** was also formed as a result of the reduction, albeit as the minor compound. To further the utility of this synthetic method, it was shown that the reaction conditions are tolerant

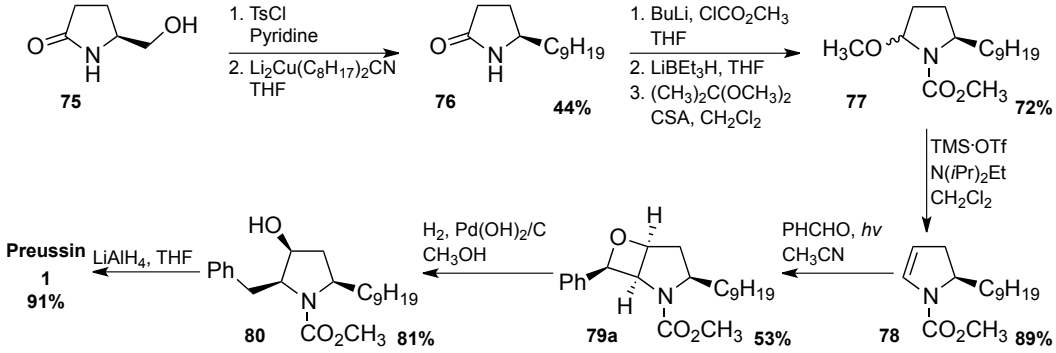
of a range of ketones, aldehydes and amines to give a series of preussin analogues.[29] Bertrand and Wolfe also synthesised preussin in a flexible fashion, with the key step in their synthesis being the construction of the pyrrolidine ring through a Pd-catalysed carboamination (Scheme 9).[30] This method allowed for the simultaneous construction of the bond between C3 and N as well as the installation of the benzyl group, which was shown to be tolerant towards a large range of aryl species.



Scheme 9: *The efficient synthesis of preussin from Draper and Britton and Bertrand and Wolfe's novel Pd catalysed carboamination*

A common trend from the selected examples above was that the syntheses of preussin (**1**), and many other pyrrolidine alkaloids, often rely upon the construction of the pyrrolidine ring late in the synthesis once other functional groups have been already installed and defined. An alternative strategy for the synthesis of pyrrolidine alkaloids would be by starting with the 5-membered ring in place initially. This approach has been demonstrated in the work by Bach and co-workers in their use of 2-pyrrolidones as a starting point for a diastereoselective Paternò−Büchi reaction (Scheme 10).[31-33] They demonstrated the transformation of commercially available L-pyroglutaminol **75** to the 5-nonyl derivative **76** through organocuprate chemistry, followed by the careful reduction of the lactam to hemiaminal **77** and elimination dehydration to 2-pyrroline **78**. A [2+2] photochemical reaction (a Paternò−Büchi reaction) with 2-pyrroline **78** and benzaldehyde (**56**) delivered a 22:5 mixture of bicyclic diastereomers **79a**/**79b** that were readily separable. The major compound

was reduced to give the monocyclic pyrrolidine **80**, which was reduced further to give preussin (**1**). The other bicyclic diastereomer **79b** was also reduced to give a diastereomer of preussin.



Scheme 10: *Bach and co-workers synthesis of preussin from a 2-pyrrolidone*

With the concept of producing pyrrolidine alkaloids from a pre-existing nitrogen heterocycle, the development of methodologies that allow for the generation of pyrrolidine molecules from aromatic pyrrole (**81**) are perceived as valuable. Pyrrole (**81**) is the electron rich aromatic analogue of pyrrolidine, containing the 4-carbons and single nitrogen found in the pyrrolidine skeleton. Taking advantage of the nucleophilicity of the aromatic pyrrole, selective aromatic substitution of the ring is possible before dearomatisation to unmask the pyrrolidine structure. However, while known, the dearomatisation of pyrrolic species is not trivial and is often complicated by undesirable side reactions due to the pyrroles high electron density. As with other aromatic systems however, the removal of aromaticity in the pyrrole molecule can be achieved in two possible ways; reduction or oxidation. These will be discussed in detail in the following section.

1.2 Methods for the dearomatisation of pyrrole

1.2.1 Reductive Methods

The first of the two potential processes for the dearomatisation of the pyrrolic systems to be discussed will be the various reduction chemistries associated with pyrrole (**81**). Pyrrole (**81**) is an electron-rich aromatic heterocycle, therefore performing a reduction (i.e. the gain of electrons) is a process that is challenging, being non-selective and often requires harsh reaction conditions. The following section will detail the two pathways of reduction in pyrrolic systems; the full reduction, and the partial reduction of pyrrole (Figure 3).

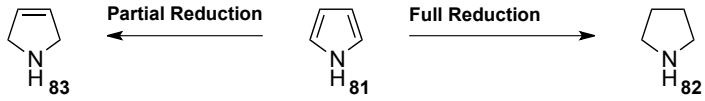
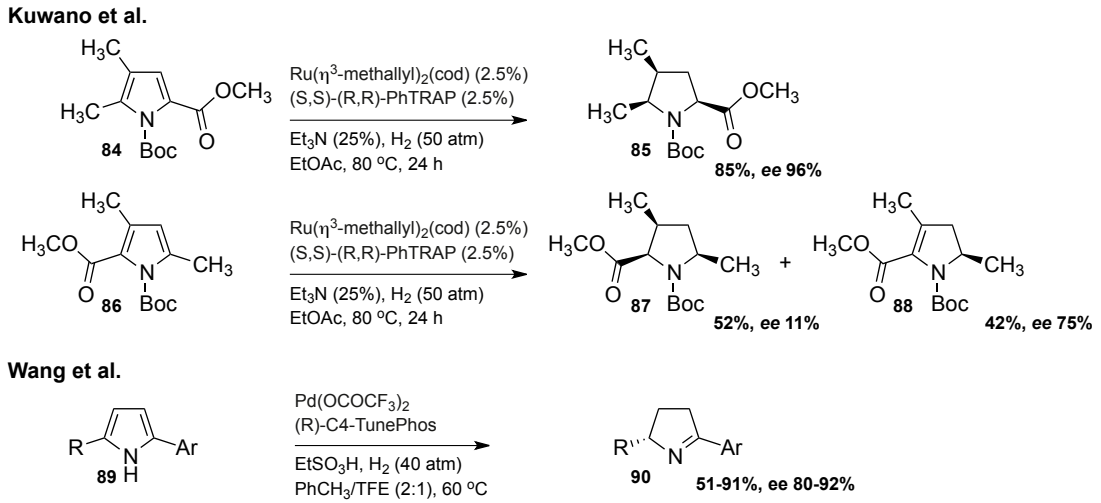


Figure 3: *The scope of the reduction of pyrrole*

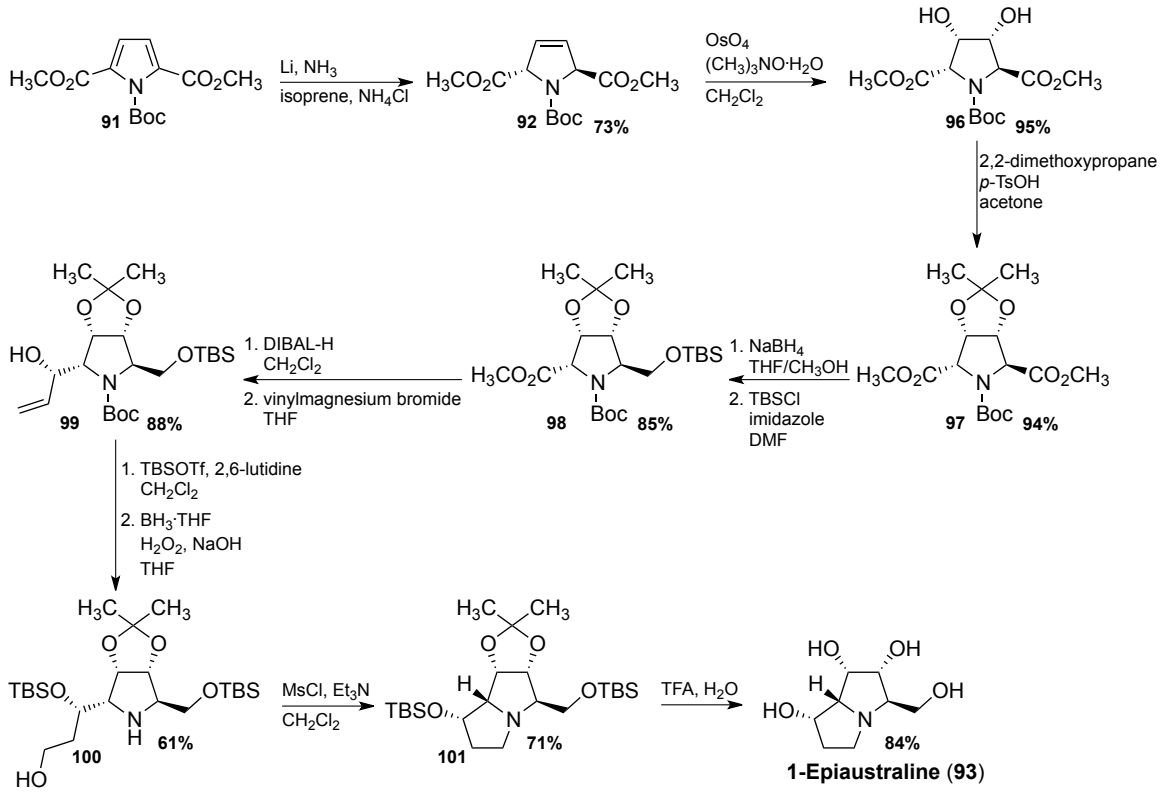
Similar to benzene that can be reduced to the saturated cyclohexane, the reduction of pyrrole (**81**) can occur to lead to the saturated pyrrolidine (**82**). This process of reduction will be referred to as the "full reduction" in the remainder of the body of this work.

The full reduction of pyrrole (**81**) to the saturated pyrrolidine (**82**) is difficult (as with most aromatic systems), often giving mixtures of saturated and partial reduction products, but it can be performed *via* catalytic hydrogenation with a Pt catalyst,[34,35] Ni catalyst,[36,37] and Pd catalyst,[38] however high temperatures and pressures are often required for these processes. For a long time there has not been any advancement on the catalytic hydrogenation of pyrrole and it is often avoided due to the mixture of products. However, Kuwano and co-workers have recently developed an enantioselective hydrogenation of tri-substituted pyrroles (**84**) with a Ru catalyst (Scheme 11).[39] The products of the method developed by Kuwano are dependent upon the substituents on the pyrrole ring, still resulting in a mixture of complete and partial reduction products from some pyrrole starting materials. Towards controlling the reduction through catalytic hydrogenation, Wang and co-workers have achieved an enantioselective synthesis using an enantiomerically pure palladium catalyst in an acidic medium to selectively generate partially reduced aryl functionalised pyrroles (**90**), a method that has a high tolerance of functionality (Scheme 11).[40] Unfortunately, the utility of the full reduction of pyrrole is limited in the targeting of pyrrolidine natural products, as demonstrated by the fact that only a handful of syntheses for structurally simple pyrrolidine like natural products exist.[41-45]



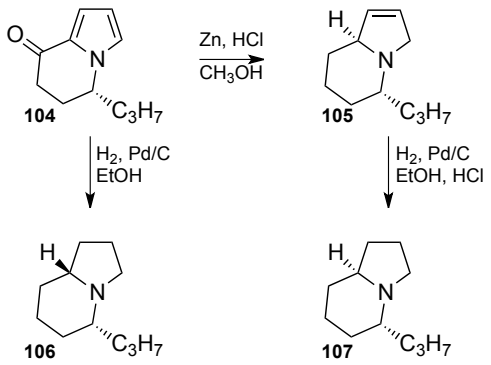
Scheme 11: *Contemporary examples of the reduction of pyrrole*

In contrast to the full reduction of pyrrole (**81**), the partial reduction of pyrrole is a powerful tool in targeting pyrrolidine alkaloids, as demonstrated by the greater number of total syntheses featuring this transformation. The partial reduction of pyrrole can lead to a 3-pyrroline (**83**) that features an alkene between C3 and C4 that allows for further functionalisation post reduction. When considering the partial reduction of an aromatic system the Birch reduction is a common example. This is a powerful reaction that is performed with the electrons generated from the electride salt of alkali metals such as sodium and lithium in liquid ammonia. The Birch reduction is often preformed in the presence of an alcohol, which acts as a convenient proton source for the unstable ionic intermediate. Mechanistically, the first step of the Birch reduction is the acceptance of an electron by the aromatic ring, which conceptually requires an electron poor aromatic ring to favour the electron donation. As such, electron rich aromatic systems such as pyrrole prove to be poor candidates for the Birch reduction and significant modifications to the parent heterocyclic system need to be considered.[46] Donohoe and co-workers have demonstrated that when substituted with electron withdrawing groups at the 1-, 2- and 5-positions, pyrrole **91** underwent reduction using the Birch conditions to the 3-pyrroline **92**.[47] This strategy was further used by the Donohoe group in the total synthesis of racemic 1-epiaustaline (**93**) (Scheme 12),[48-50] hyacinthacine A1(**94**)[50,51] and omuralide (**95**),[52] in which the formation of the alkene of the 3-pyrroline was vital for the incorporation of the hydroxyl substituents.



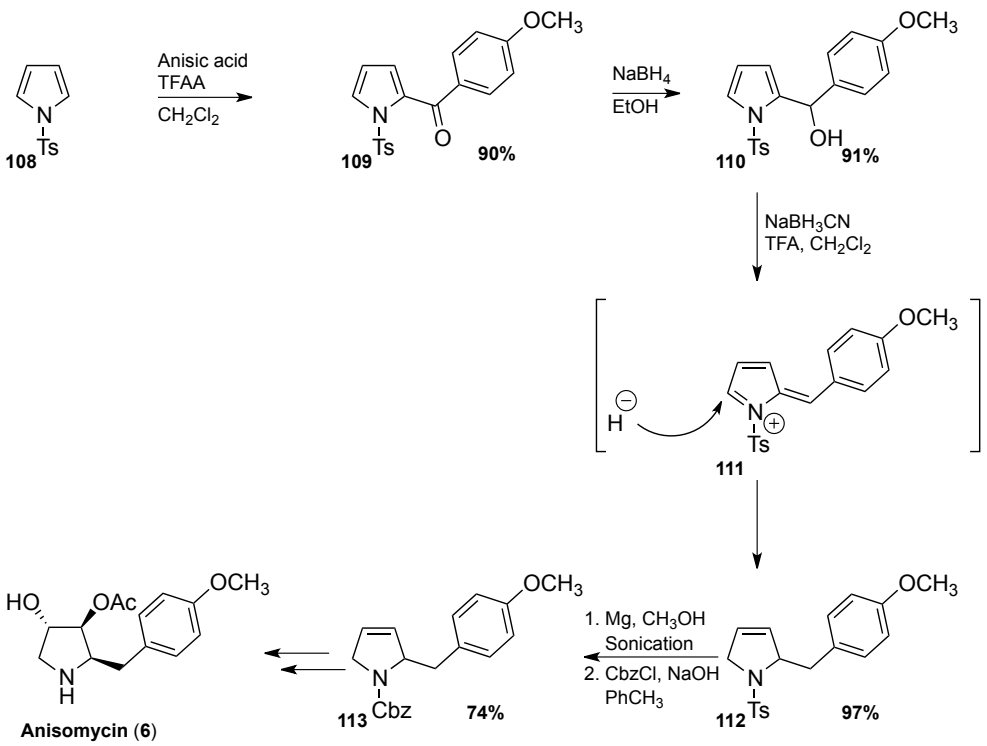
Scheme 12: *Donohoe's synthesis of 1-epiaustraline, demonstrating the utility of the Birch reduction on electron poor pyrrolic systems*

A method more amenable with electron-rich pyrroles is that of the Knorr−Rabe partial reduction of pyrroles.[53] This method has been reported only a few times since its initial report in 1901, which is possibly due to the harsh reaction conditions of heating the starting pyrrole to reflux in 5 M aqueous HCl with zinc metal. The initial report was on the reduction of the electron rich 2,5-dimethyl pyrrole **102** with a more recent example by Schumacher and Hall reducing the 2-benzyl pyrrole **103** to an intermediate exploited for the synthesis of anisomycin (**6**).[54] Recently however, this methodology has been applied to α-ketopyrroles in a modified reaction matrix with methanol as the solvent at reflux and the slow addition of solid zinc and concentrated HCl.[55] These modified conditions have been applied to the reduction of bicyclic α-ketopyrroles (**104**) to their 3-pyrroline analogues (**105**), and it was observed that the opposite stereochemistry at C2 was obtained compared to that of catalytic hydrogenation of pyrrole **104** to the completely reduced pyrrolidine **106** (Scheme 13). While the initial conditions described by Knorr and Rabe were improved upon, the reaction conditions still posed an issue with pyrroles that contain acid or thermal sensitive functionalities such as an ester or other labile functional groups.



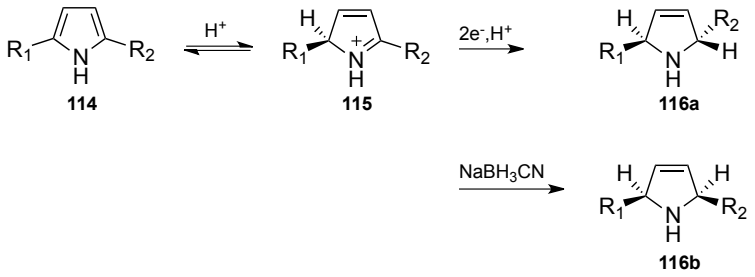
Scheme 13: *The stereochemical outcome of the Knorr-Rabe partial reduction of pyrrole, as improved upon by Gourlay and co-workers*

While the previously described methods for pyrrole reduction showed some clever engineering and modifications to the reaction conditions, a common issue remained. Namely, the harsh reaction conditions required for the reduction of the pyrrole often led to poor conversion or to decomposition. A milder reduction processes first reported by Ketcha and co-workers used sodium cyanoborohydride in an acidic medium.[56] This method required the use of the moderately electron deficient *N*-tosylpyrrole (**108**), where the tosyl group removes electron density away from the pyrrole. In contrast to the mechanism of the Birch reduction where the first step was the acceptance of an electron by the pyrrole ring before protonation by a suitable proton source, the Ketcha method generates an ionic iminium species from the addition of a proton to the pyrrole ring before this species is reduced by the hydride source. This mechanism was similar to that proposed for the Knorr−Rabe partial reduction. You and co-workers demonstrated that this reductive methodology was applicable to the reduction of α-ketopyrrole **109** to yield 3-pyrroline (**112**), which has led to an elegant interception in the synthesis of racemic anisomycin (**6**) (Scheme 14).[57] While α-ketopyrroles can be reduced directly to the 3-pyrroline by this method, the first step where the reduction of the ketone takes place is the rate-determining step. This prevents the reduction proceeding when the ketone is in further conjunction with a second aromatic group, and as a result needs to be independently reduced by sodium borohydride in ethanol. Alcohol **110** can then be treated with sodium cyanoborohydride in TFA/dichloromethane to produce 3-pyrroline **112** in excellent yield.



Scheme 14: *The partial reduction of an electron deficient pyrrole with $NaBH_3CN$, utilised in the partial synthesis of anisomycin, as demonstrated by You and co-workers*

Interestingly, the modified method reported by You gave the opposite stereochemistry to that of the modified Knorr−Rabe reduction by Gourlay. When 2,5-disubstituted pyrroles (**114**) were reacted, the Knorr−Rabe reduction resulted in a *trans*-relationship across these two substituents, while the borohydride reduction yielded the *cis*-isomer. This result was justified by the comparative reaction mechanisms of both of the reductions (Scheme 15). The first step in both reductions resulted in an iminium ion intermediate (**115**) that was the result of and acidic proton adding to the electronically dense pyrrole ring. In the Knorr−Rabe reduction, the iminium ion intermediate was reduced by the electrons generated by the dissolving metal to give the more thermodynamically favoured *trans*-product **116a**. This outcome can further be explained by Zn coordinating to the iminium ion and blocking the least hindered face of the ring, forcing protonation to occur on that face.[55] In the cyanoborohydride reduction the iminium ion intermediated was reduced by attack of the hydride to the less sterically hindered face of the ring, producing the *cis*-product **116b**.



Scheme 15: *The mechanistic justification for the stereochemical result in partial reduction chemistries*

As demonstrated above, the reduction of pyrrole through full or partial reduction methods supports the aim of using pyrrole as a starting material in the synthesis of pyrrolidine alkaloids. However, the reductive methods are limited in their scope, allowing only relatively electronically-poor pyrrolic species to undergo partial reduction or being forced to use harsh acidic conditions to facilitate the desired reaction. This results in an over reliance on electron-withdrawing protecting groups that lead to more synthetic steps and sometimes challenging protecting group removal. The addition of electrons to an electron rich molecule is the inherent limitation of this approach and, as such, oxidative methods may be more broadly applicable for the dearomatisation of pyrrole.

1.2.2 Oxidative Methods

While the concept of the reduction of pyrrole (**81**) is well founded, the oxidation of pyrrole proves to be much less common. Given the high electron density of the ring, pyrrole can potentially undergo oxidation to synthetically useful 2-pyrrolinones (**117**), however, pyrrole has a reputation as a molecule that decomposes *via* uncontrolled polymerisation under oxidative conditions (Figure 4). For pyrrole itself, this polymerised material is often referred to as "pyrrole black" or "polypyrrole" and as the former name suggests is a black, tarry substance.[58] This is not to say that polypyrrole is an entirely undesirable product as it was one of the first organic semi-conducting polymers to be discovered and controlled methods of polymerisation are still sort after in materials chemistry.[59,60] Furthermore, the importance of polypyrrole can be highlighted by the Nobel Prize in Chemistry in 2000, which was awarded to Alan J. Heeger, Alan G. MacDiarmid and Hideki Shirakawa for the "discovery and development of conductive polymers".[61] On the other hand, as a useful synthetic process enabling the synthesis of small molecules, polypyrrole is not a desirable

product. As such, methods for the controlled oxidation of pyrrole to 2-pyrrolinone are valuable.

As alluded to above, pyrroles (**81**) can be oxidised to valuable 2-pyrrolinones (**117**), commonly observed with the double bond across the C3 and C4 positions (however, alkene functionality at the C4 and C5 position is also known). This oxidative transformation will herein be referred to as the "controlled oxidation" of pyrrole. These 2-pyrrolinones have the potential to serve as powerful intermediates in the synthesis of pyrrolidine natural products as well as biologically active pyrrolidones; compounds that are of equal synthetic interest as pyrrolidines. However, due to the unreliable nature of pyrrole under oxidative conditions, this strategy has yet to be extensively explored, with efforts towards the controlled oxidation of pyrrole resulting in varying levels of success.

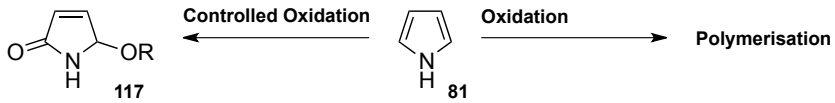
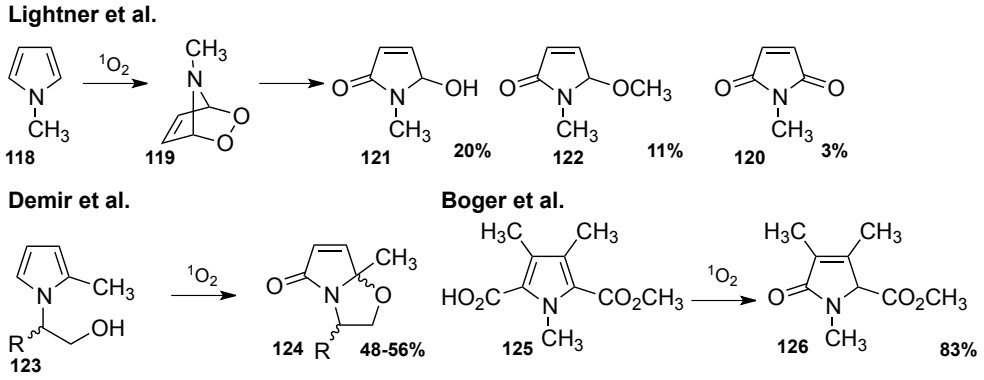


Figure 4: *The scope of the oxidation of pyrrole*

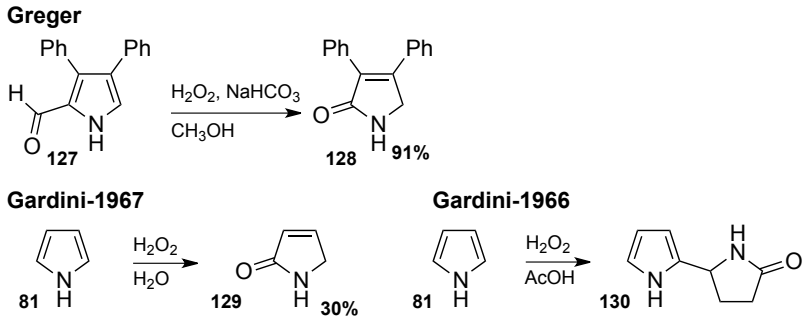
The first, and perhaps most significant method to be widely adopted for the process of the controlled oxidation of pyrroles (**81**) was with singlet oxygen ($^1O_2$). While this method of pyrrole oxidation often produces large amounts of decomposition, it has been reported that 5-hydroxy- and 5-alkoxy-2-pyrrolinones can be produced.[62-64] It should be noted that in the majority of reported accounts on pyrrole oxidation with $^1O_2$ the oxidant was a result of the photochemical excitation of O_2 and rarely *via* the decomposition of a highly oxygenated chemical species. As outlined in work conducted by Lightner and co-workers, $^1O_2$ can add to pyrrole **118** in a [4+2] hetero Diels-Alder reaction to give an unstable *endo*-peroxide intermediate **119** (Scheme 16).[65] Due to its instability this *endo*-peroxide decomposes rapidly to maleimide **120** or the 5-hydroxy-2-pyrrolinone **121**. Reactions performed in methanol also produce the 5-methoxy-2-pyrrolinone **122** as part of the reaction mixture, presumably by the formation of an intermediate iminium ion or by direct nucleophilic attack on the *endo*-peroxide. Furthermore, the nucleophilic attack can occur intramolecularly, resulting in a bicyclic system (**124**).[66-68] As shown by Boger and co-workers the photo-oxidative decarboxylation of highly functionalised pyrrole 2-carboxylic acids

(**125**) gives good to excellent yields of a single product (**126**).[69] This has worked well in some interesting total syntheses towards various isochrysohermidins,[70,71] with the added benefit of being able to predict the regiochemical outcome.



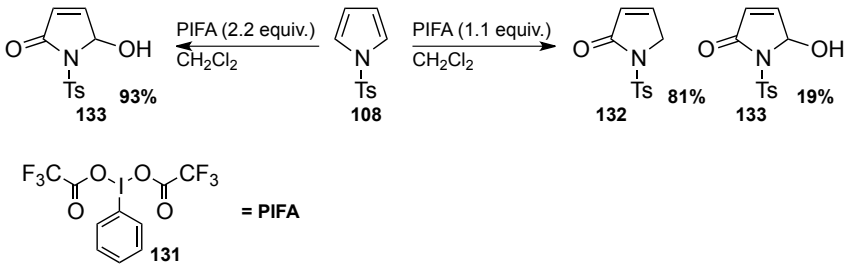
Scheme 16: *The $^1O_2$ oxidations of Lightner, Demir and Boger*

Other strategies to generate 2-pyrrolinones through oxidation of pyrrolic systems have been employed that use more traditional oxidants such as peroxides. As with Boger's decarboxylative oxidations that yield a single product, Pichon-Santander and Scot have employed the Bayer−Villeger oxidation with H_2O_2, followed by hydrolysis and rearrangement on pyrrole 2-carbaldehydes (**127**).[72] This has also been used by Coffin and co-workers and improved upon by Greger and colleagues (Scheme 17).[73,74] While strategically these syntheses are interesting as the aldehyde governs the regioselectivity of the product 2-pyrrolinone, they again suffer from having to have an aldehyde starting material in the first place that was eliminated upon reaction. It is worth noting that without a cleavable group such as an aldehyde or carboxylic acid, the reaction of an unfunctionalised pyrrole with hydrogen peroxide proceeded to produce the 2-pyrrolinone **129** in low yields as shown by Gardini,[75] and when this reaction was performed in an acidic medium then 5-(2-pyrrolyl)-2-pyrrolidone **130** was produced (Scheme 17).[76,77]



Scheme 17: *The Bayer-Villeger oxidation of pyrrole from Greger and co-workers, and the initial H_2O_2 oxidation studies from the Gardini group*

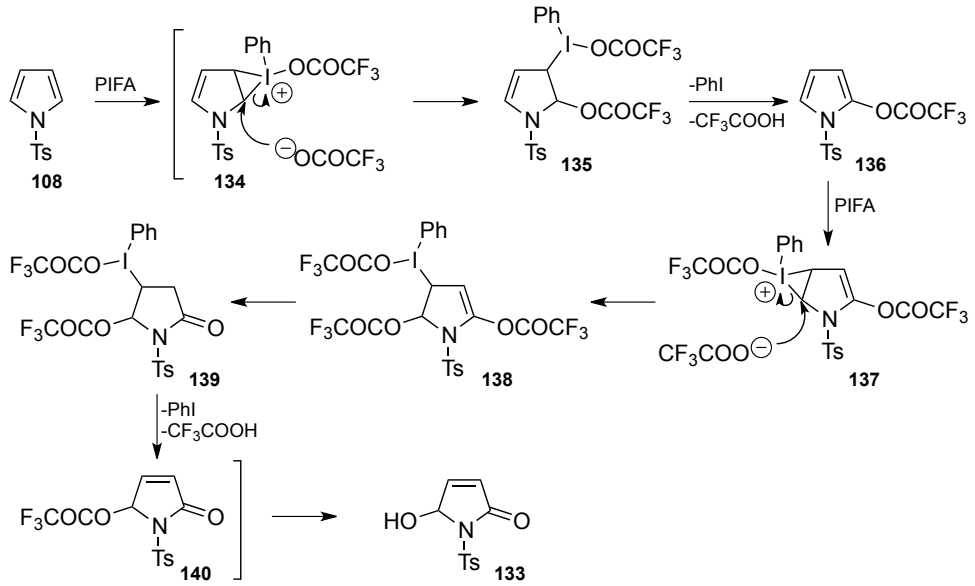
More recently hypervalent iodine species have been used as oxidants in conjunction with pyrroles, and in some cases have oxidised the pyrrole to desirable 2-pyrrolinones. In 2010, Alp and co-workers reported a controlled oxidation of the electron deficient *N*-tosylpyrrole **108** with the hypervalent iodine reagent phenyliodine bis(trifluoroacetate) (PIFA) (**131**) in dry dichloromethane.[78] It was reported that with a single equivalent of the reagent, quantitative conversion was achieved with the major product being 1-tosyl-1H-pyrrol-2(5H)-one (**132**) in an 81% yield and the minor product 5-hydroxy-1-tosyl-1H-pyrrol-2(5H)-one (**133**) in a 19% yield. When the reaction conditions were altered such to employ two equivalents of the oxidant they observed 5-hydroxy-1-tosyl-1H-pyrrol-2(5H)-one (**133**), with a 93% isolated yield (Scheme 18).



Scheme 18: *Alp and co-workers reported oxidation of N-tosylpyrrole with PIFA*

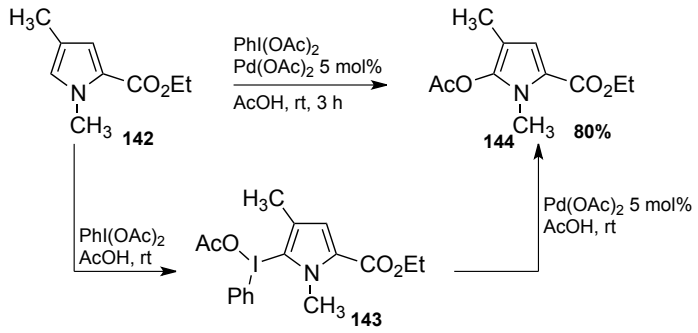
Alp and co-workers proposed a mechanism for their oxidation where PIFA directly added across the C2 and C3 double bond of the pyrrole to give the iodonium ion **134** (Scheme 19). A dissociated trifluoroacetate ion was suggested to attack the C2 position forcing iodonium migration to C3. Elimination of the iodonium from C3 gave pyrrole **136**, which was proposed to be either hydrolysed directly to give 2-pyrrolinone **132** or was subsequently reacted in the same way across the double bond

at C4 and C5 with a second unit of PIFA to give iodonium ion **137**. It was postulated that intermediate **138** underwent hydrolysis before elimination of the iodonium at C4 to give 5-trifluoroacetoxy-2-pyrrolinone **140**, which yielded 5-hydroxy-2-pyrrolinone **133** upon *in situ* hydrolysis.



Scheme 19: *The proposed mechanism by Alp and co-workers for their oxidation of N-tosylpyrrole with PIFA*

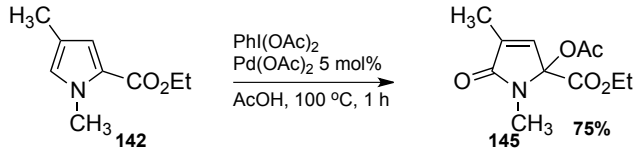
Lubriks and Suna demonstrated the use of phenyliodine diacetate (PIDA) (**141**) with $Pd(OAc)_2$ in acetic acid to selectively mono-acetoxylate a range of relatively electron-rich and electron-deficient pyrroles (**142**) in good to excellent yields (Scheme 20).[79]



Scheme 20: *Lubriks and Suna's work on the acetoxylation of pyrrole via catalytic palladium rearrangement of an iodonium*

They were able to isolate the intermediate iodonium pyrroles (**143**) before subjecting them to palladium-catalysed rearrangement at room temperature to generate the

acetoxy pyrroles (**144**). Furthermore, on heating the reaction to 100 °C, mimicking conditions established by Crabtree,[80] they found that some substrates returned 2-pyrrolinones (**145**) and sometimes maleimides (Scheme 21).



Scheme 21: *The oxidation of N-arylpyrrole as reported by Suna and Lubriks, under the reaction conditions established by Crabtree*

1.3 The general strategy for the thesis

While the controlled oxidation of pyrroles has yet to be as fruitful as the partial reduction of pyrrole as a practical synthetic method, there are apparent advantages in oxidation compared to reduction. Of the oxidation examples above, many of the pyrroles involved are electron-rich and have very few functional groups initially present, yet there are also electron-poor examples suggesting that the controlled oxidation of pyrrole may be more practical than that of the partial reduction methodologies and have a larger scope. It was also apparent that the molecule produced in all cases, the 2-pyrrolinone (**117**), possessed more functionality to manipulate post dearomatisation than the 3-pyrroline product (**83**) of the partial reduction methodologies. The 3-pyrroline products from the partial reduction of pyrrole can only be further modified with manipulation of the alkene, whereas the 2-pyrrolinone products can foreseeably allow for additional options, including nucleophilic addition to the carbonyl, nucleophilic addition to the C5 position of the ring as well as taking advantage of the electronic bias of the α, β-unsaturated lactam for selective alkene modifications (Figure 5).

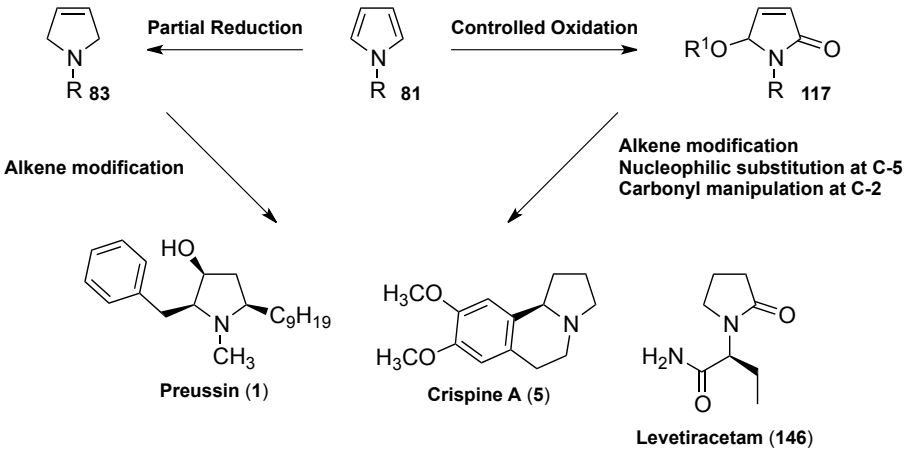


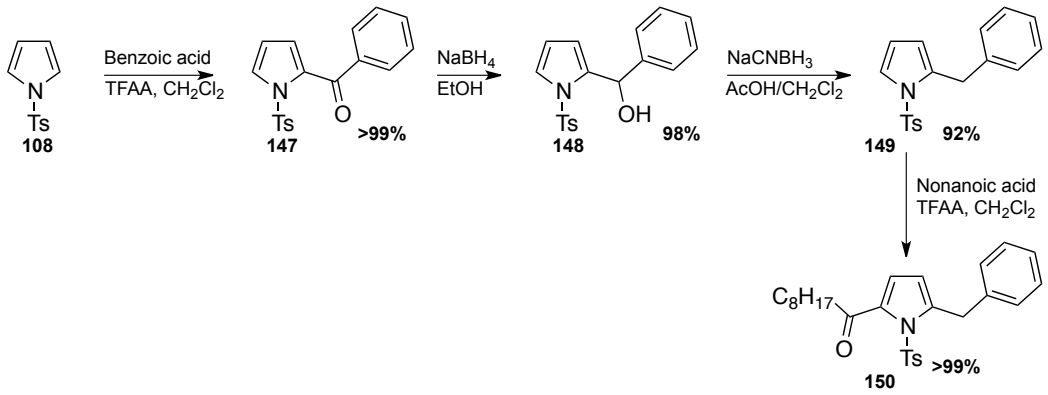
Figure 5: *Visualising the larger diversity of synthetic handles available post controlled oxidation compared to that post partial reduction*

The above introduction should demonstrate the synthesis of pyrrolidine alkaloids is significant and that the concept of using pyrrole as a molecular template serves well in synthesising these targets. Whereas reduction methodologies have been used exclusively when targeting pyrrolidine alkaloids from pyrrole, the oxidation of pyrrole has not been developed into a widespread method, despite its potential for highly functionalised advanced intermediates towards pyrrolidine alkaloids. As such, the following body of work details efforts to develop new synthetic methodologies in the controlled oxidation of pyrroles towards 2-pyrrolinones. This methodology will be incorporated into the synthetic strategy for constructing pyrrolidine alkaloids such as preussin (**1**) and codonopsinine (**3**) and also 2-pyrrolidinones derivatives of biological importance such as levetiracetam (**146**), a known anticonvulsant medication used in the treatment of epilepsy patients.

Chapter 2 – Investigations Towards Controlled Oxidation

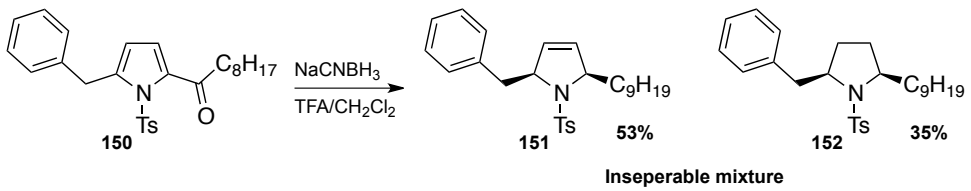
2.1 Partial reduction of pyrrole towards preussin

A previous investigation undertaken at the University of Tasmania in 2010 by the author demonstrated the further utility of the partial reduction chemistry of pyrrole in targeting pyrrolidine alkaloids, focusing on preussin (**1**).[81] During this study, a practical synthesis of the pyrrolidine target was not achieved as a result of limitations of the partial reduction chemistry - this led to the investigation into optimising the synthesis.



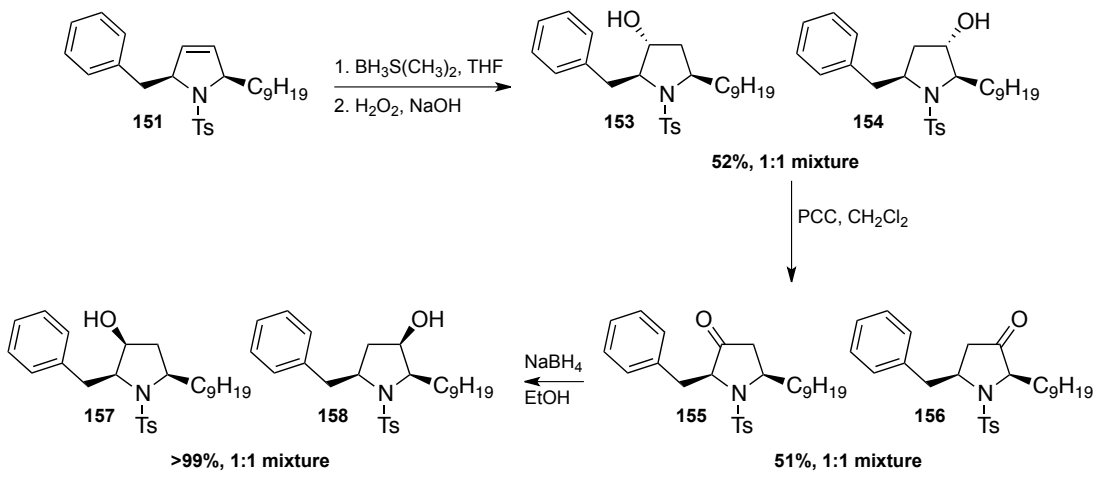
Scheme 22: *The rapid synthesis of an α-keto-trisubstututed pyrrole, ready for partial reduction chemistry*

Towards the synthesis of preussin (**1**), the α-keto-trisubstituted pyrrole (**150**) was synthesised in 4 steps from *N*-tosylpyrrole (**108**) in a 90% overall yield to install the required carbon framework (Scheme 22). Pyrrole **150** was subjected to partial reduction conditions developed by You[57] to give the desired 2-benzyl-5-nonyl-1-tosyl-3-pyrroline **151** having *cis*-stereochemistry with respect to the substitution at the C2 and C5 positions in a 53% yield (Scheme 23). This yield was lower than anticipated with the remainder of the reaction mixture consisting of decomposition products and the saturated pyrrolidine **152**. Shorter reaction times and few equivalents of cyanoborohydride were both investigated; however, no further improvement upon the reaction conditions was found. Furthermore, this mixture was inseparable by silica column chromatography so the next steps in the synthetic sequence were undertaken on the mixture of **151** and **152**. The ratio of the two products was estimated by integration of the ^{1}H NMR spectrum of the mixture of compounds.



Scheme 23: *The partial reduction on the trisubstituted pyrrole, resulting in the desired cis-pyrrolidine* ***151***

The next step in the proposed synthesis was to install a single hydroxyl group selectively at the C3 position of the pyrroline ring. This was achieved through hydroboration-oxidation chemistry, which added a BH_3 across the double bond with a boron−carbon bond forming at the least substituted carbon of an alkene that was oxidised *in situ* to an alcohol. However, the reaction proceeded to give a 1:1 mixture of the 3-monohydroxylated pyrrolidine **153** and 4-monohydroxylated pyrrolidine **154** (Scheme 24), indicating no steric bias between the C3 and C4 carbon of 3-pyrroline **151**. No steric bias was found even when a bulky borane such as 9-BBN was used. Unfortunately, the mixture of alcohols **153** and **154** were inseparable by both standard silica and reverse phase column chromatography, yet the completely reduced pyrrolidine **152** could be isolated at this point. As expected the oxidation chemistry delivered the hydroxyl group with *trans*-stereochemistry in relation to the previously installed functional groups. Initially, the Mitsunobu reaction was attempted to invert the stereocentre of the hydroxyl group, but under the reaction conditions E2 elimination likely occurred, producing 3-pyrroline **142**, effectively setting the synthesis back two steps. This stereochemistry was eventually corrected by oxidation of the alcohols **153** and **154** to the ketones **155** and **156** with PCC, before reduction to the alcohols **157** and **158** with sodium borohydride, which allows for hydride nucleophilic attack on the least hindered face of the pyrrolidine ring, forcing the desired all *cis*-stereochemistry (Scheme 24). With the relative stereochemistry corrected the compounds were still, unsurprisingly, not separable by chromatography.

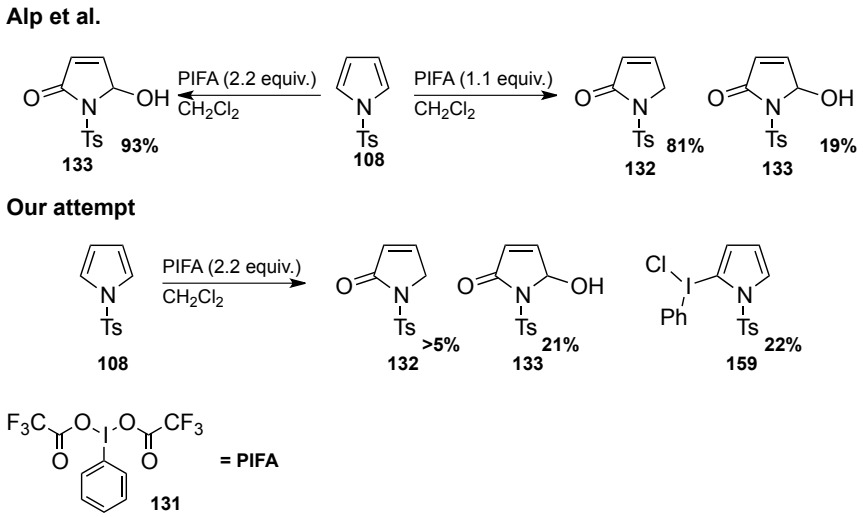


Scheme 24: *Hydroboration-oxidation of **142** followed by a correction of stereochemistry. The structure of the 4-regioisomers has been omitted for simplicity*

While the partial reduction methodology had proven to be quite useful in the synthesis of several natural products in the past, the demonstrated lack of selectivity across the double bond of the 3-pyrroline affects the method from being particularly useful when considering 2,3,5-trisubstituted pyrrolidines. This conclusion, coupled with the reduction methodology only being effective for electron-deficient pyrroles led to the decision to investigate methods for the controlled oxidation of pyrrole, which would result in a 2-pyrrolinone. It was perceived that this approach would serve better for a wider range of targets as the resulting 2-pyrrolinone would contain, among other functionality, an α, β-unsaturated amide that can undergo more selective addition reactions due to the bond polarisation.

2.2 The hypervalent iodine oxidation of electron-rich pyrroles

Initial oxidation trials were focussed on the method reported by Alp and co-workers, which suggested the use of PIFA (**131**) in varying amounts would selectively deliver the desirable 2-pyrrolinones from *N*-tosylpyrrole (**108**).[78] Alp reported that *N*-tosylpyrrole (**108**) in the presence of a single equivalent of PIFA (**131**) gave 2-pyrrolinone **132** and a minor amount of 2-pyrrolinone **133**, while two equivalents of PIFA resulted in only the formation of 2-pyrrolinone **133** (Scheme 25).



Scheme 25: *The oxidative method reported by Alp and co-authors in comparison to the results observed from our attempts*

However, when the oxidation conditions described by Alp were followed with two equivalents of the oxidant **131**, a mixture of three products resulted (Scheme 25). These products were isolated and identified as the two oxidation products described by Alp and the 2-iodoniumpyrrole **159**. The 2-iodoniumpyrrole **159** was primarily identified in the ^{1}H NMR spectrum by the three resonances at 6.40, 6.76 and 7.48 ppm representing the C3, C4 and C5 protons of a 2-substituted pyrrole respectively. The triplet at 6.40 ppm had a coupling constant of 3.3 Hz, which is typical of the coupling between the protons of C3 and C4, giving strong evidence of a 2-substituted pyrrole.[82] Further evidence of iodine substituted at the C2 position was observed in the ^{13}C NMR spectrum of the compound, which had a diagnostic resonance at 93.04 ppm that is characteristic of this kind of pyrrolic system.[82] Initially, 2-iodoniumpyrrole **159** was assigned as containing trifluoroacetate covalently bound to the iodine rather than chlorine, however this was found to not be the case after not being able to identify a resonance in the ^{19}F NMR spectrum or a resonance in the ^{13}C NMR for the CF_3. A low resolution X-ray structure[†] was collected that further suggested that there was indeed no trifluoroacetate in the molecule and it was likely a

[†] Crystal structure data collections of **159** were attempted on the colourless needles using the MX2 beamline of the Australian Synchrotron. The crystals showed remarkable damage in the X-ray beam, changing from straight and colourless to bent and brown within 20 seconds of beam exposure. Remarkably, a solution to the structure could be obtained from this limited data using the program *SUPERFLIP*[83] in CRYSTALS.[84] The use of Fourier difference maps allowed for the generation and partial positional refinement of the structure. The refinement confirmed the connectivity of the molecule, which is shown in Figure 6, but allows for no further discussion or conclusions. Attempts to refine the structure using isotropic or anisotropic models failed, due to the low quality dataset.

halogen present, however any crystal collected did not have the integrity to withstand the full X-ray data collection process (Figure 6).

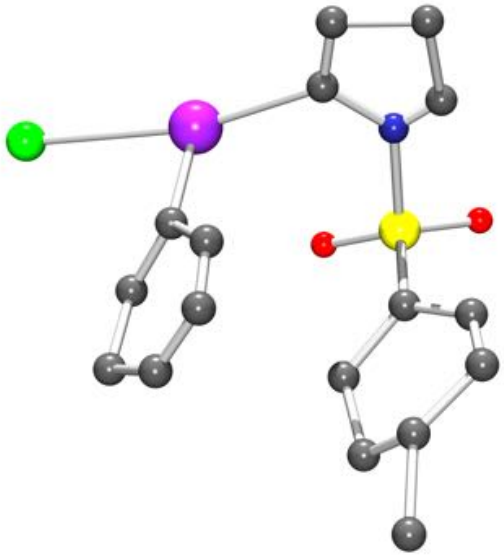
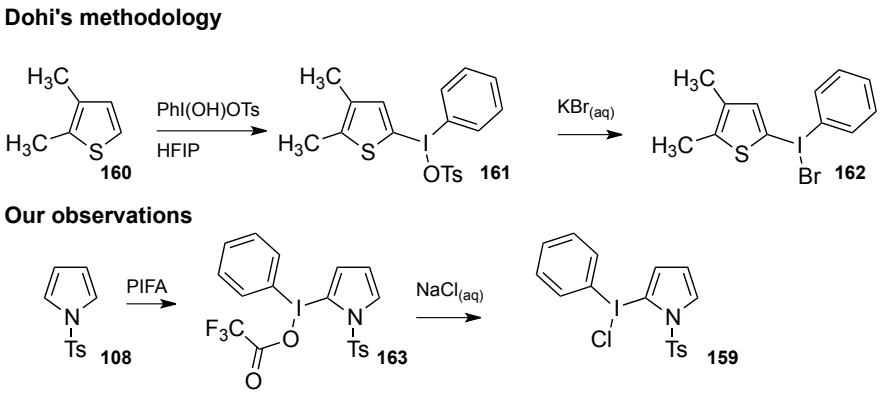


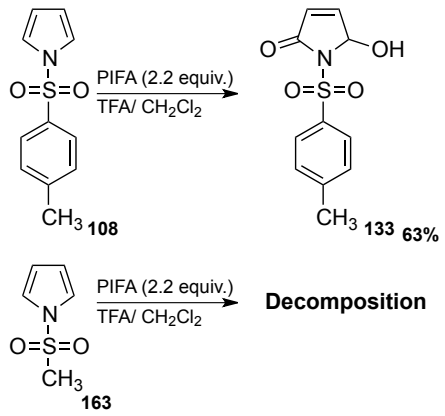
Figure 6: *Low resolution X-ray crystal structure of* ***159***

A silver nitrate halogen test was conducted on 2-iodoniumpyrrole **159**, and produced a positive test for a chlorine anion. While only a qualitative technique, this coupled with the reaction conditions strongly suggested the chloride salt was present. On workup of the reaction, a saturated aqueous sodium chloride solution wash was performed after the extraction that may have introduced the chloride by anion exchange. This anion exchange on an iodonium is common, as shown by the example from Dohi and co-workers in their production of various aryl and heteroaryl iodonium salts (Scheme 26).[85-87]



Scheme 26: *An example of anion exchange on an iodonium salt as developed by Dohi and co-workers as a reference for the chloride salt observed from the PIFA reaction*

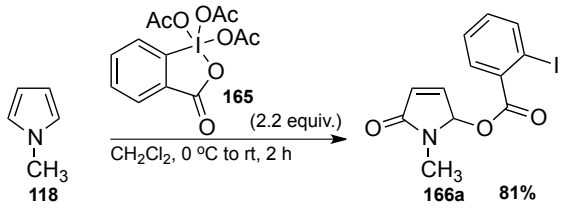
While the discovery of 2-iodoniumpyrrole **159** was indeed interesting it was found to not be an intermediate in the oxidation reaction when resubjected to the proposed oxidation conditions, and as such it was suggested to be from an alternative reaction pathway. The reaction was also attempted with just a single equivalent of the oxidant and the same reaction mixture was observed, albeit in lower yield. As with what was described by Alp and co-workers, the reaction was performed at room temperature, however, a similar result was found when the reaction mixture was cooled to 0 °C, and also when the reaction mixture was heated to reflux. Furthermore, moisture sensitivity was briefly investigated, with no difference in the reactivity found from using bench grade dichloromethane over dry solvent. Both acetic acid and TFA were investigated as alternative solvents or co-solvents to use in the oxidation. There appeared to be no reaction when acetic acid was used as the solvent and mixtures of TFA/dichloromethane produced complex mixtures of products. However, when the reaction was performed in neat TFA there was a significant result - on reaction with 2.2 equivalents of PIFA (**131**) in neat TFA, *N*-tosylpyrrole (**108**) was converted to the 5-hydroxy-2-pyrrolinone **133** in a 63% yield (Scheme 27). While this result was excellent, when the starting pyrrole was changed to the electronically similar *N*-methanesulfonylpyrrole (**164**) a complex product mixture was again observed. Furthermore, subjecting the electron-rich *N*-methylpyrrole (**118**) to any of the oxidative conditions with PIFA (**131**) resulted in complex mixtures and decomposition products.



Scheme 27: *The controlled oxidation of N-tosylpyrrole with PIFA in TFA*

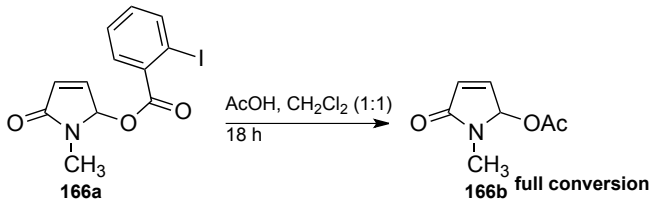
In investigating the pyrrole oxidation methodology with hypervalent iodine oxidants, PIDA (**141**) was also examined as an alternative oxidant. On reaction with *N*-tosylpyrrole (**108**) and *N*-methylpyrrole (**118**), PIDA produced mixtures that were very complex by ^{1}H NMR spectroscopy and TLC with a poor mass balance. As with PIFA, it was concluded that PIDA was a poor choice of oxidant due to the complex product mixtures observed so attention was turned to another hypervalent iodine, the Dess−Martin periodinane (**165**).[88,89]

As with previous oxidation trials, both *N*-tosylpyrrole (**108**) and *N*-methylpyrrole (**118**) were both treated with one equivalent of Dess−Martin periodinane (**165**) in dichloromethane at room temperature. Both reactions were monitored by TLC over a 3 h period and while oxidation of *N*-tosylpyrrole did not occur (returning only starting material), a single product was observed on reaction with *N*-methylpyrrole. This compound was assigned as the 5-aroyloxy-2-pyrolinone **166a** and was obtained in a 31% yield. On modification of the reaction conditions, *N*-methylpyrrole was slowly added to a chilled solution of the oxidant as it was postulated that this order of addition would limit any potential oxidative polymerisation. Also, 2.2 equivalents of Dess−Martin periodinane was used relative to *N*-methylpyrrole as from the assigned structure it was clear that two units of the oxidant were participating in the reaction. The reaction mixture was warmed to room temperature over 2 h before being reductively quenched with a saturated solution of sodium metabisulfite and washed with sodium hydrogen carbonate to remove iodobenzoic acid to yield **166a** in an 81% yield (Scheme 28).



Scheme 28: *The reaction of N-methylpyrrole with Dess−Martin periodinane*

Surprisingly, the product of the Dess−Martin periodinane oxidation featured an *ortho*-iodobenzoyloxy moiety at C5, which was unusual, as other literature oxidations with the Dess−Martin periodinane (**165**) do not report the incorporation of the oxidant into the product. It should also be noted that only trace amounts of the 5-acetoxy-derviative **166b** were ever observed in the ^{1}H NMR spectrum of the crude material, which was a result of the *in situ* generation of **166a**, and then exchange with acetic acid. This postulate was supported by an experiment in which the 5-aroyloxy-2-pyrrolinone **166a** was stirred in a 1:1 mixture of dichloromethane/acetic acid and full conversion to the 5-acetoxy-2-pyrrolinone **166b** was observed over 18 h (Scheme 29).



Scheme 29: *Conversion of 5-aroyloxy-pyrrolinone **166a** to 5-acetoxy-2-pyrrolinone **166b***

The structural assignment of 5-aroyloxy-2-pyrolinone **166a** was supported in the ^{1}H NMR spectrum primarily by the diagnostic resonances at 6.30, 7.09 and 6.65 ppm, assigned to the protons at the C3, C4 and C5 positions on the ring respectively (Figure 7). The resonance at 7.09 ppm appeared as a doublet of doublets that coupled with the doublet resonance at 6.30 ppm with a coupling constant of 6.0 Hz, which is appropriate for a *cis*-alkene. The second coupling constant calculated from the resonance at 7.09 ppm was 1.2 Hz, which likely resulted from coupling with the resonance at 6.65 ppm that does not express a well resolved splitting pattern in either a 300 or 400 MHz spectrometer.

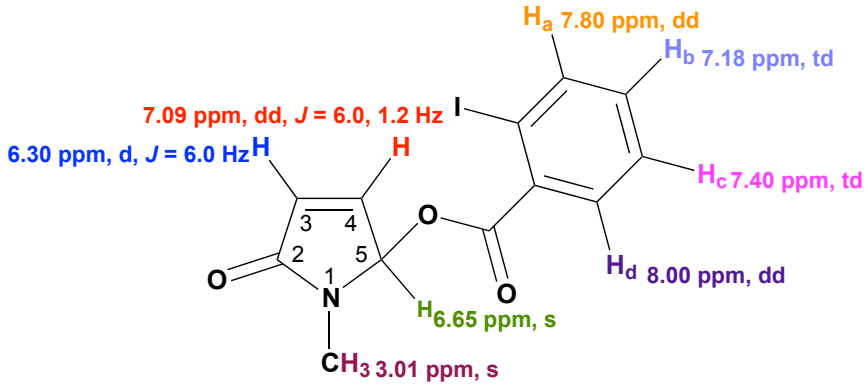


Figure 7: *Assignment of the protons from the ^{1}H NM spectrum of* ***166a***

The coupling and arrangement around the ring was supported by correlations observed within the COSY spectrum, with a correlation observed between the resonances at 7.09 ppm and 6.65 ppm (Figure 8).

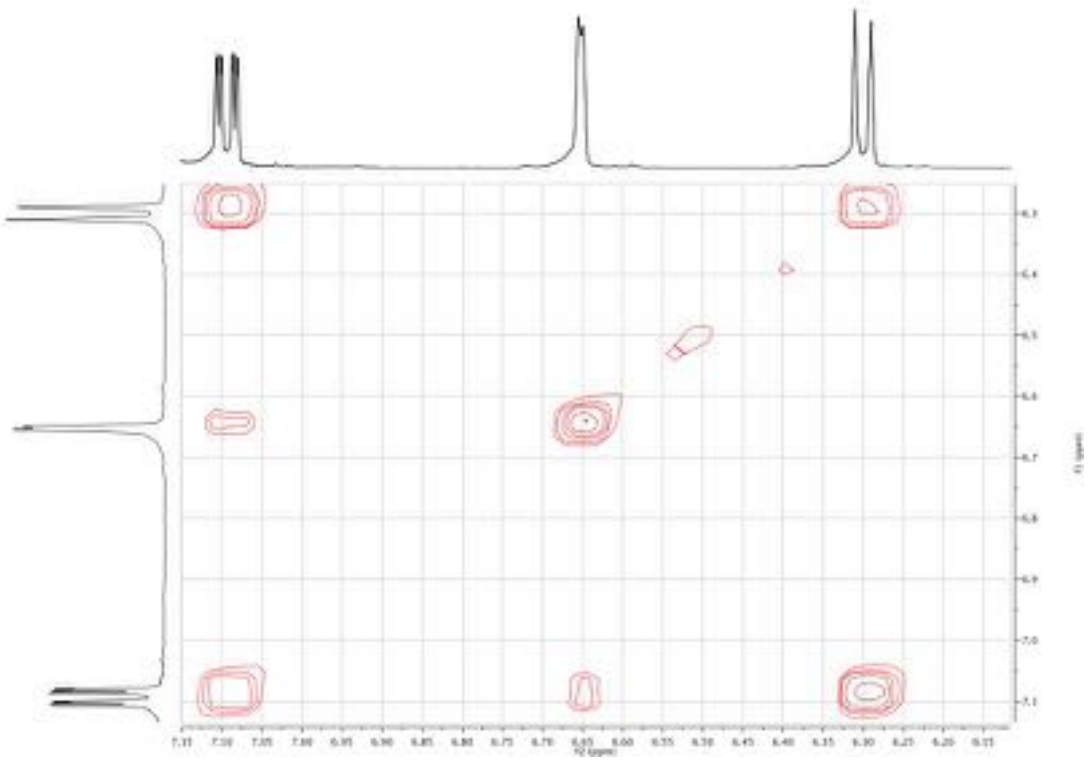


Figure 8: *COSY spectrum illustrating the correlations between the protons of the 2-pyrolinone ring*

Further to the assignment of the protons around the 2-pyrrolinone ring, the ^{1}H NMR spectrum gave support for an *ortho*-disubstituted benzene present in the molecule (Figure 7). Four resonances appeared in the aromatic region of the ^{1}H NMR spectrum that collectively displayed the classic splitting patterns associated with

ortho-disubstituted benzene (i.e. two sets of doublets of doublets and two sets of triplets of doublets). The resonances that were observed experimentally for these protons matched that of what was predicted such that the resonances at 7.80, 7.18, 7.40 and 8.00 ppm were assigned as protons **a**, **b**, **c** and **d**, respectively (Figure 7).[82] Furthermore, there was evidence to support *ortho*-iodobenzoate functionality and amide functionality from the ^{13}C NMR spectrum with two separate resonances appropriate for carbonyl resonances observed at 165.9 ppm and 170.1 ppm. Diagnostic stretches were also observed in the IR spectrum. An X-ray crystal structure was obtained on recrystallisation of the oxidation product **168** of *N*-(*p*-methylbenzyl)-pyrrole (**167**) (Table 1 - entry **E**) that categorically supported the assigned structure of the oxidation (Figure 9).

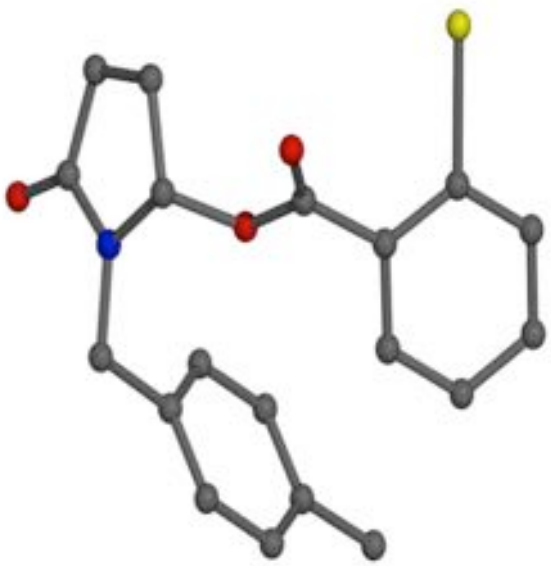


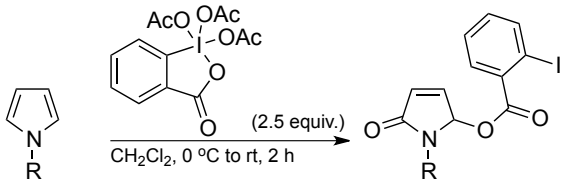
Figure 9: *X-ray crystal structure of the 2-pyrrolinone oxidation product* ***168*** *of N-(p-methylbenzyl)-pyrrole* ***167***

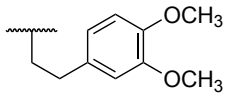
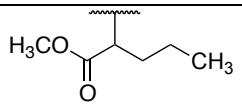
After a rapid solvent screening for the oxidation of pyrrole with Dess−Martin periodinane, dichloromethane was found to be the solvent that produced the cleanest result. Significantly, on analysis of the crude reaction mixture by ^{1}H NMR, the reaction proceeded cleanly with no evidence to suggest polymerisation or decomposition, which was controlled by the slow addition of pyrrole to a high concentration of the oxidant. As previously described, using a single equivalent of

Dess−Martin periodinane (**165**) with *N*-methylpyrrole (**118**) resulted in the formation of the 5-aroyloxy-2-pyrrolinone **166a** in a 31% yield rather than a mono-oxidised 2-pyrrolinone, indicating that any intermediate species was more reactive, and consumed faster, than the starting pyrrole **118**. ^{1}H NMR experiments were performed to identify other intermediate products or a potential mono-oxidised thermodynamic product by cooling to −78 °C and monitoring the sample as the temperature increased to room temperature. Unfortunately, on the NMR time scale no extra resonances were observed except those consistent with the 5-aroyloxy-2-pyrrolinone **166a** and the starting material **118**. The same result was observed when the experiment was repeated with a large excess (20 equivalents) of pyrrole added to the oxidant. Furthermore, it was observed that trace amounts of water helped facilitate the reaction, as demonstrated in the comparison of bench grade solvent to anhydrous solvent under a nitrogen atmosphere (81% yield compared to 65% yield under anhydrous conditions). This observation was similar to, and supported by, previous oxidations with Dess−Martin periodinane in which trace amounts of water help promote the oxidation of alcohols due to partial hydrolysis of the oxidant to a more reactive form.[90]

Following this exciting result, a range of *N*-alkyl pyrroles were oxidised with the Dess−Martin periodinane reagent (**165**) under the developed conditions to yield the corresponding 5-aroyloxy-2-pyrrolinones in good to excellent yields (Table 1). Both electron-rich *N*-alkyl and *N*-aryl pyrroles were well tolerated (entries **A**-**H**), however *N*-tosylpyrrole (**108**) (entry **I**) and 1-methyl-pyrrole-2-methylcarboxylate (**180**) (Table 2 - entry **A**) both returned starting material on workup. This result was conceivably due to the lower electron density present in these pyrroles as a result of the electron withdrawing properties of the *N*-substituents. The parent pyrrole **81** (entry **H**), while low yielding still converted cleanly to the corresponding 5-aroyloxy-2-pyrrolinone **179** in a 56% yield, which was a significant result as pyrrole itself is particularly susceptible to polymerisation and decomposition under oxidative conditions.

Table 1: *The Dess−Martin periodinane oxidation of a range of N-substituted pyrroles*

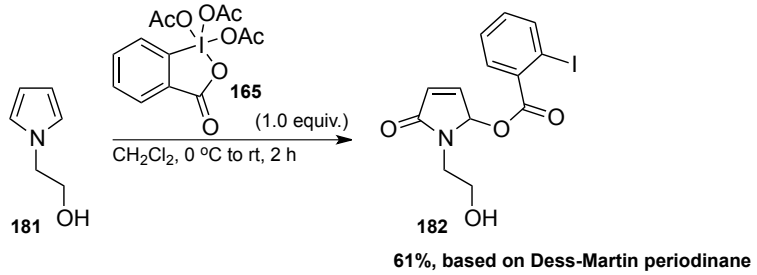


Entry	Pyrrole	-R	Product	Yield
A	**118**	-CH_3	**166a**	81%
B	**169**	-CH_2CH_3	**170**	83%
C	**171**	-*p*-C_6H_4-CH_3	**172**	88%
D	**173**	-*p*-C_6H_4-OCH_3	**174**	93%
E	**167**	-CH_2-C_6H_4-CH_3	**168**	93%
F	**175**		**176**	96%
G	**177**		**178a/178b**	88% (1:1 mixture of diastereoisomers)
H	**81**	-H	**179**	56%
I	**108**	-*p*-toluenesulfonyl	**-**	0%

When the *N*-substituent on pyrrole had a stereogenic centre a 1:1 mixture of diasteroisomers was produced, as exemplified in the oxidation of pyrrole **177**, producing the diastereomeric mixture of 2-pyrrolinones **178a** and **178b** (Table 1 - entry **G**). Compounds of this type, which can be synthesised in two steps from readily available amino esters, could be further studied for the asymmetric synthesis of natural products or drug-like molecules.

The Dess−Martin periodinane reagent (**165**) is commonly used to oxidise primary and secondary alcohols to aldehydes and ketones respectively,[90,91] and as a

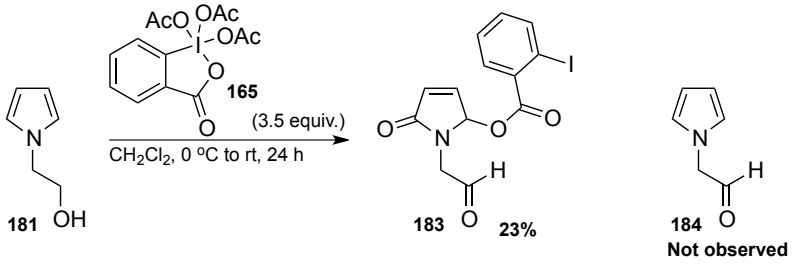
competitive oxidation, 1H-pyrrole-ethanol (**181**) was subjected to the oxidative reaction conditions. Interestingly, when this pyrrole was treated under the standard reaction conditions with one equivalent of Dess−Martin periodinane, the 5-aroyloxy-2-pyrrolinone **182** with the alcohol functionality still intact was the major product in a 61% yield based upon Dess−Martin periodinane (Scheme 30). This result was determined by analysis of the ^{1}H NMR spectrum of the crude material, which displayed the diagnostic 1H resonances associated with the protons around the 2-pyrrolinone ring at 6.28, 6.83 and 7.10 ppm instead of the two sets of 2H triplets observed at 6.17 ppm and 6.71 ppm that are found in the starting pyrrole. Additionally, a broad singlet was observed at 3.05 ppm, which was constant with a –OH proton resonance and the four protons of the ethanol chain were all identified. However, the most convincing piece of evidence for selective pyrrole oxidation was the lack of a resonance in the ^{1}H NMR spectrum for the aldehyde that would be anticipated from primary alcohol oxidation. Further to this, the ^{13}C NMR spectrum only contained two resonances that could be assigned to a carbonyl group.



Scheme 30: *Selective oxidation of pyrrole **181***

When 1*H*-pyrrole-ethanol (**181**) was subjected to the reaction conditions over a longer reaction time with 3.5 equivalents of Dess−Martin periodinane (**165**) in relation to the pyrrole, it was oxidised to the aldehyde **183** in a low 23% yield (Scheme 31). The formation of aldehyde **183** was identified in the ^{1}H NMR spectrum as a sharp singlet at 9.57 ppm, with standard 2-pyrrolinone resonances also being observed in the spectrum. The low yield observed suggested that the compound was relatively unstable under the oxidative conditions, and the alcohol should be protected if it was to become a practical synthesis. Remarkably, it should be noted that at no time was the aldehyde-tethered pyrrole **184** observed as a product under the oxidation conditions. This suggested that the reactivity of pyrroles towards Dess−Martin periodinane was clearly higher than that of primary alcohols towards

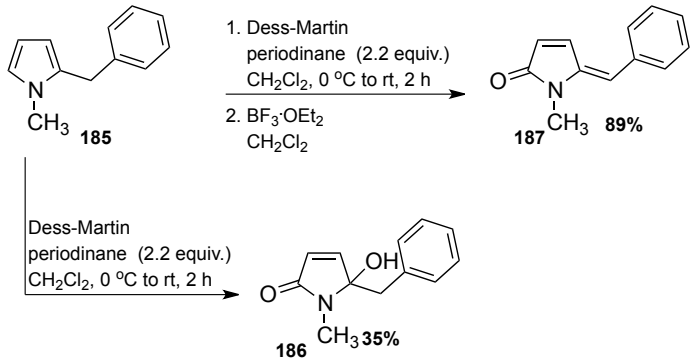
the oxidant, resulting in the selective oxidation of pyrrole in the presence of alcohol functionality.



Scheme 31: *On longer reaction times pyrrole **181** was oxidised to aldehyde **183**, however aldehyde **184** was not observed.*

The oxidation of pyrroles with Dess−Martin periodinane (**165**) was further applied to the oxidation of selected 2-substituted pyrroles (Table 2). As previously commented on, *N*-methyl-pyrrole-2-methylcarboxylate (**180**) did not undergo oxidation with Dess−Martin periodinane (likely due to the electron-deficient pyrrole not reacting as a result of the electron-withdrawing character of the methyl ester functionality). However, the initial oxidation of 2-benzyl-*N*-methyl pyrrole (**185**) with Dess−Martin periodinane did proceed. On purification, this reaction gave the 5-benzyl-5-hydroxy-2-pyrrolinone **186** in a 35% yield (Scheme 32). This product was a result of the steric bulk of the alkyl group installed at the C2 position of pyrrole **185**, and it was proposed that the 5-aroyloxy functionality was initially produced in the resultant 2-pyrrolinone but was quickly hydrolysed from the aroyloxy to alcohol **186** to alleviate the steric strain. It should be noted that the 5-aroyloxy-intermediate was never identified in the ^{1}H NMR of the crude reaction mixture. On workup of the oxidation, the crude yield was much higher than that of the purified compound and by the ^{1}H NMR spectrum there appeared to be much more product in the crude material than was eventually isolated from column chromatography. This then suggested that the 5-hydroxy-2-pyrrolinone **186** was relatively unstable on silica. To avoid this significant decrease in yield an *in situ* reduction of the hydroxyl group was attempted with $BF_3{\cdot}EtO_2/Et_3SiH$.[92] This well known reduction would produce a *N*-acyliminium ion on treatment of 5-hydroxy-2-pyrrolinone **186** with a Lewis acid, which would in turn be reduced by triethylsilane. However, rather than reduction, elimination proved more favourable under these reaction conditions resulting in the alkene **187** as a single isomer, which was chromatographically stable and isolated in an 89% yield

over the two steps (Table 2-Entry **C**). With this result, successive eliminations were performed with only the Lewis acid, as the triethylsilane was not necessary.



Scheme 32: *Oxidation of 2-benyzl-N-methylpyrrole (**185**) with Dess−Martin periodinane*

The ^{1}H NMR spectrum of 5-hydroxy-2-pyrrolinone **186** displayed two sets of doublets at 2.88 ppm and 3.24 ppm coupling to each other with a coupling constant of 13.7 Hz that is typical of geminal coupling for protons attached to the sp^{3} carbon of a benzyl group. Further to this, the two doublet resonances at 5.86 ppm and 6.81 ppm had a coupling constant of 6.0 Hz, which is consistent with the protons of the alkene of the 2-pyrrolinone ring seen previously. Additionally there were resonances consistent with the aromatic protons of the benzyl group as well as a singlet at 2.90 ppm assigned as the methyl group, however, there was no evidence of the aroyloxy functionality seen in the *N*-substituted pyrroles and it was later supported by IR spectroscopy and mass spectrometry that there was an alcohol present. For the 5-benzylidene-2-pyrrolinone **187**, the ^{1}H NMR spectrum had simplified significantly from 5-hydroxy-2-pyrrolinone **186**. There was a resonance at 6.72 ppm that was expressed as a doublet of doublets with the large 6.0 Hz coupling constant, consistent with a proton of the alkene of the 2-pyrrolinone; however, the other alkene proton was hidden under the aromatic resonances of the benzylidene system. The proton associated with the alkene of the benzylidene system appeared as a resonance at 6.42 ppm. This proton resonance displayed a strong nOe correlation with the methyl singlet at 3.21 ppm in the NOESY spectrum of the compound. As such, the NOESY analysis supported the formation of the *E*-isomer of the alkene, as the *Z*-isomer would involve the benzylidene proton correlating to the C4 alkene proton, which was not observed. This assignment was categorically supported by an X-ray crystal

structure (Figure 10). This was a significant finding as previous reports of the synthesis of this compound have been as 1:1 mixtures of the *E*- and *Z*-isomers.[93]

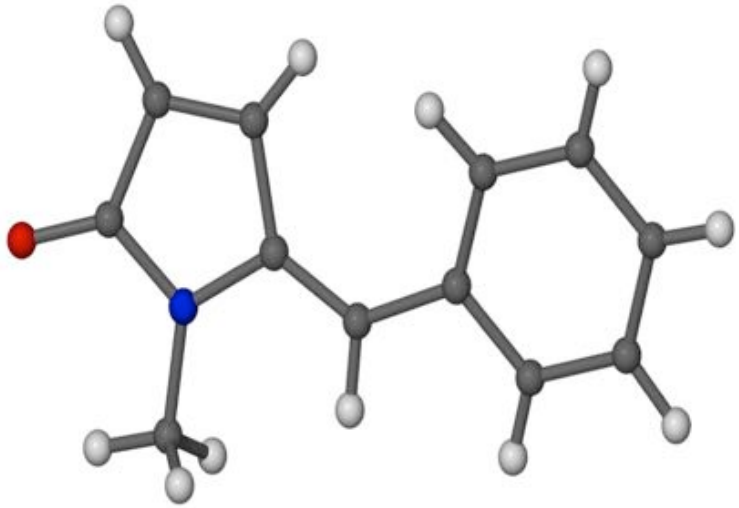
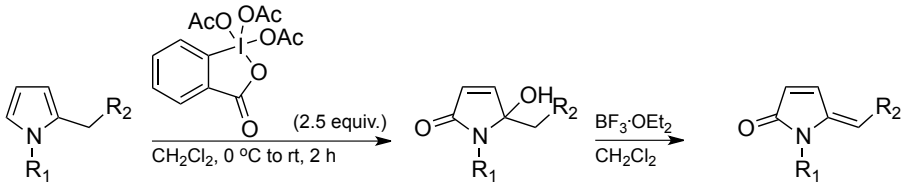


Figure 10: *X-ray crystal structure of* ***187***

The two step oxidation/elimination process was also performed on 2-ethylpyrrole **188** and 2-nonylpyrrole **190** (Entries **D** and **E**) as well as the 2-methyl-*N*-benzyl pyrrole **192** (Entry **F**), resulting in the desired alkenes in almost quantitative yields, across two steps (Table 2).

Table 2: *The Dess−Martin periodinane oxidation of a range of 1,2-disubstituted pyrroles*

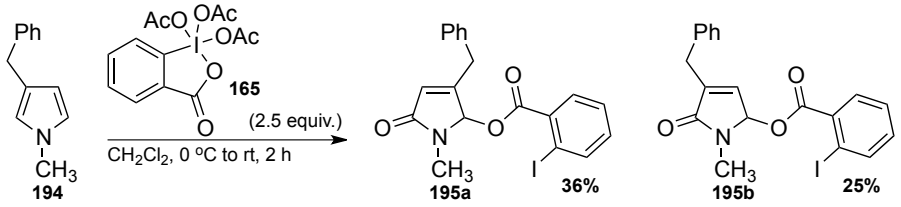


Entry	Pyrrole	Method*	R_1	R_2	Product	Yield
A	**180**	A	$-CH_3$	$-CO_2CH_3$	-	0%
B	**185**	A	$-CH_3$	$-C_6H_5$	**186**	35%
C	**185**	B	$-CH_3$	$-C_6H_5$	**187**	89%
D	**188**	B	$-CH_3$	$-CH_3$	**189**	>95%
E	**190**	B	$-CH_3$	$-n-C_8H_{17}$	**191**	>95%
F	**192**	B	$-CH_2-C_6H_4-CH_3$	$-CH_3$	**193**	>95%

*Method A: Dess−Martin periodinane (2.5 equiv.), CH_2Cl_2. Method B: 1.) Dess−Martin periodinane (2.5 equiv.), CH_2Cl_2. 2.) BF_3•OEt_2, CH_2Cl_2.

Next, the oxidation conditions were extended to other substitution patterns on the pyrrole ring. When subjected to the oxidation conditions, 3-benzyl-*N*-methylpyrrole (**194**) yielded a 3:2 mixture of regioisomeric 2-pyrrolinones **195a** and **195b** respectively in a combined 61% yield (Scheme 33). These two regioisomers were separated by column chromatography on silica gel and analysed by ^{1}H NMR to assess the substitution patterns of the products. The major compound was found to have two separate pyrrolidinone resonances at 5.89 ppm and 6.66 ppm that were assigned as the proton at C5 and the proton at C3 respectively. These two resonances were observed as singlets and from that assignment the two protons were not adjacent to each other due to the lack of splitting. That meant that the aroyloxy functionality was likely adjacent to the benzyl functionality as seen in compound **195a**. Analysis of the ^{1}H NMR spectrum of the minor compound provided evidence to suggest that the benzyl group was adjacent the carbonyl of the amide of the 2-pyrrolinone. This was due to the resonance at 6.49 ppm that was assigned to the

alkene proton being split by the resonance of the C5 proton at 6.54 ppm, placing these two protons adjacent to each other as seen in compound **195b**.



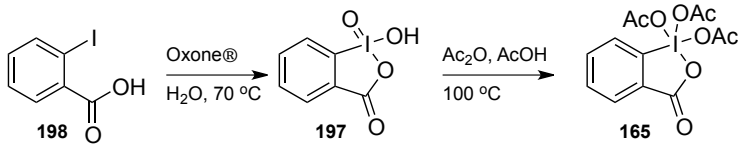
Scheme 33: *The oxidation of the 3-benzylpyrrole **193** under the developed Dess−Martin periodinane conditions*

As a final examination of the substrate scope of this new controlled oxidation of pyrroles, 2,5-dimethyl-*N*-benzylpyrrole **196** was treated with Dess−Martin periodinane under the standard conditions. Unsurprisingly, the reaction returned a poor crude yield of a complex mixture of unidentified products, which was likely due to the oxidation to the lactam not being possible in this substrate.

2.3 The IBX controlled oxidation of N-methylpyrrole

The controlled oxidation of pyrroles with Dess−Martin periodinane (**165**) was an exciting addition to the arsenal of substrates that can be oxidised with this reagent. As an expansion of this research, the synthetic precursor to the Dess−Martin periodinane (**165**), IBX (**197**) was also investigated for the controlled oxidation of pyrrole. IBX (**197**) is readily available from the oxidation of 2-iodobenzoic acid (**198**) with Oxone® in water and can be converted to Dess−Martin periodinane through reaction with acetic anhydride (Scheme 34).[94] While these two oxidants have comparable reactive properties and outcomes, IBX is not as frequently used due to its insolubility in many common organic solvents with reactions often being performed in DMSO. IBX is considerably lower in molecular weight than the Dess−Martin periodinane (280.02 $gmol^{-1}$ for IBX, compared to Dess−Martin at 424.14 $gmol^{-1}$), rendering it a more atom-economical oxidation agent. This, in addition to the higher cost of Dess−Martin periodinane[‡] highlighted IBX as an appropriate hypervalent iodine reagent to investigate for the oxidation of pyrroles.

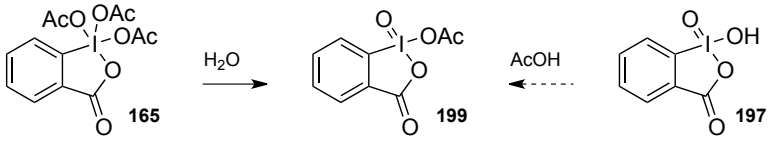
[‡] Dess−Martin periodinane $136/5 g, 2-iodobenzoic acid $129/100 g, Oxone® $93.50/1 kg, as sourced from Sigma−Aldrich online cataloged accessed 25th January 2015



Scheme 34: *The contemporary synthesis of IBX and Dess−Martin periodinane from 2-iodobenzoic acid*

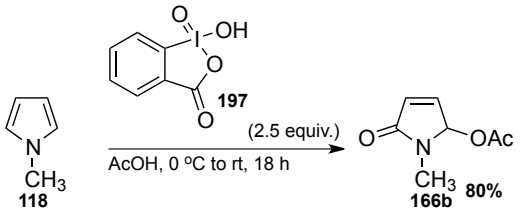
Initial reactions focused on finding a suitable solvent that IBX (**197**) was soluble enough in to perform the desired oxidation chemistry. Common solvents for IBX oxidations include both DMSO and acetonitrile, both of which were tested yet neither gave a positive result for the pyrrole oxidation. Dichloromethane was also tested as it was postulated that while the solubility of IBX may be low in this solvent, enough of the oxidant would solubilise to allow for the oxidation chemistry to proceed. Again however, this produced a negative result.

In a significant mechanistic study, Schreiber and Meyer suggest that the active species in the Dess−Martin periodinane oxidation was in fact a partly hydrolysed form of the Dess−Martin reagent.[90] This discovery came about by the observation that water helped accelerate the oxidation of alcohols and that the researchers could initially only get one of their more difficult oxidations to proceed with a two year old bottle of Dess−Martin periodinane (**165**), which was found to be mostly insoluble in dichloromethane. While not discussed by Schreiber and Meyer, it was reasonable to conclude that the insolubility was due to the Dess−Martin periodinane hydrolysing completely to IBX (**197**), while the active species was a hydrolysis product somewhere between the two known oxidants (Scheme 35). Further to this, Schreiber and Meyer isolated and characterised a compound identified as acetoxyiodinane oxide (**199**) (a mono-acetoxy derivative of IBX). This compound was isolated after water was added to Dess−Martin periodinane and when it was used as the reactant in alcohol oxidations, it was found to react much faster than the parent hypervalent iodine. From the finding of Schreiber and Meyer it was reasoned that if IBX could react *in situ* to form the active species, then the same reactivity could be achieved with IBX as with Dess−Martin periodinane towards pyrrole oxidation (Scheme 35).



Scheme 35: *Schreiber and Meyers observed generation and isolation of acetoxyiodinane oxide from the Dess−Martin periodinane and the proposed generation of the compound from IBX*

Towards this goal, IBX (**197**) was taken in glacial acetic acid and cooled to 0 °C, on which the solution solidified due to the melting point of acetic acid (~16 °C). To this solid mass was added *N*-methylpyrrole (**118**) and the reaction mixture warmed to room temperature over 18 h to give exclusively the 5-acetoxy-2-pyrrolinone **166b** in an 80% yield, after a reductive workup (Scheme 36).



Scheme 36: *The IBX controlled oxidation of N-methylpyrrole*

The proposed formation of the active species from IBX and acetic acid appeared to be slower than the oxidation itself, and as the reaction mixture would have to undergo acetic acid exchange for the aroyloxy side-chain the reaction was left for 18 h, rather than the 2 h for the oxidation with Dess−Martin periodinane (**165**). When the reaction was stoped after just 8 h there was an approximate 1:1 mixture of the 5-aroyloxy-2-pyrrolinone **166a** to that of the 5-acetoxy-2-pyrrolinone **166b**. In an attempt to use lower amounts of acetic acid and hence make the workup and neutralisation of the reaction mixture more practical, the reaction was attempted in various mixtures of acetic acid and dichloromethane. The results of these experiments showed that the reaction was lower-yielding in mixed solvent systems and the mixture of the 2-pyrrolinones **166a** and **166b** were still present, yet on longer reaction times 2-pyrrolinone **166b** did become the major product. These results suggested that the conversion of IBX was slow and requires a high concentration of acetic acid to be used as an effective oxidant of pyrroles. Due to the long exposure to a high concentration of acid, the broad utility of this particular oxidation of pyrroles

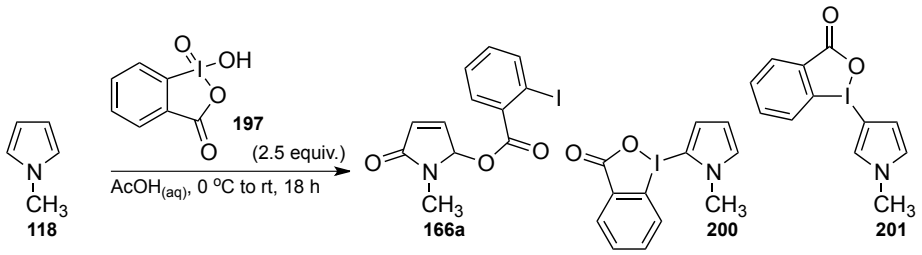
was limited to those pyrroles that were not particularly sensitive to acid; however, it did offer an alternative to the Dess−Martin periodinane oxidation by generating an active species *in situ* without having to be concerned about the instability of the Dess−Martin periodinane reagent.

In a brief examination of whether a different reactive species was in fact being generated *in situ* for the IBX oxidation, a series of NMR studies were conducted. The first study investigated the result of adding acetic acid to IBX in $CDCl_3$. A blank experiment was performed where IBX (**197**) was stirred in $CDCl_3$ for 2 h, which resulted in no resonances being observed in the aromatic region of the ^1H NMR spectrum as would be expected for IBX (Figure 11 – Spectrum **A**). This experiment was repeated with the addition of a molar equivalent of acetic acid (Figure 11 – Spectrum **B**). The ^1H NMR spectrum of this experiment now featured the 4 resonances that would be expected for the aromatic region of an IBX analogue. Further to this observation, the four resonances agreed well with the data reported by Schreiber and Meyer for acetoxyiodinane oxide (**199**), giving evidence to suggest that IBX in acetic acid does indeed generate this reactive species. A second investigation repeated these two experiments in CD_3CN, which IBX is sparingly soluble in. The blank experiment showed resonances in the aromatic region of the ^1H NMR spectrum that were consistent with IBX (Figure 11 - Spectrum **C**). However, in the experiment where acetic acid was added there was a slow appearance of a secondary set of resonances, again giving further evidence for a reactive species being formed *in situ* (Figure 11 - Spectrum **D**). Together these experiments gave support to using IBX in acetic acid to promote the oxidation of pyrrole on generation of the active oxidant, and that it was not a trivial result of IBX being soluble in acetic acid that promoted the oxidation to occour.

Figure 11: *Spectrum **A** illustrates the insolubility of pure IBX in $CDCl_3$. Spectrum **B** illustrates the reaction mixture of IBX with AcOH in $CDCl_3$, with a new set of resonances that match those resonances reported by Schreiber and Meyer for acetoxyiodinane oxide (**199**). Spectrum **C** illustrates the low solubility of IBX in CD_3CN. Spectrum **D** illustrates new resonances appearing from IBX on mixing with AcOH in CD_3CN after 2 h.*

2.4 Iodoniumpyrrolic species

An interesting observation was made under the IBX (**197**) oxidation conditions when water was added to the reaction mixture. In reactions performed in solutions of aqueous acetic acid, rather than glacial acetic acid, different reaction products were observed (Scheme 37).



Scheme 37: *Initial results of oxidation according to the IBX controlled oxidation conditions with aqueous acetic acid*

When the IBX pyrrole oxidation was performed in acetic acid with 10% H_2O the 2-pyrrolinone species was still identifiable in the ^{1}H NMR spectrum (primarily the 5-aroyloxy-2-pyrrolinone **166a**, with a trace of 5-acetoxy-2-pyrrolinone **166b**), however, extra resonances were observed, as well as an overall lower recovered crude mass. In the aromatic region of the ^{1}H NMR there was found to be a total of 14 extra proton resonances. These resonances were assigned as two independent pyrrolic compounds in the ^{1}H NMR spectrum of the crude mixture, and were separable by silica gel column chromatography.

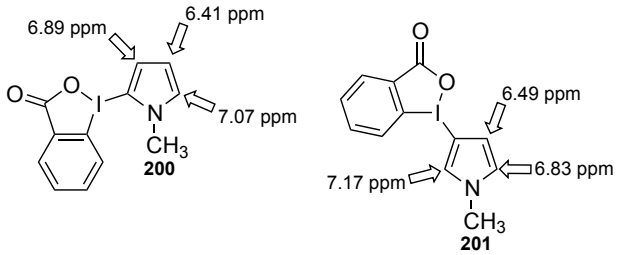


Figure 12: *Assignment of pyrrolic protons on iodoniumpyrrole **200** and **201***

Thorough analysis of the ^{1}H NMR spectrum for each of the two substituted pyrrolic compounds revealed the 2-substituted pyrrole **200** as the major compound, and the 3-substituted pyrrole **201** as the minor compound. Analysis of the 2-substituted pyrrole **200** showed three pyrrolic resonances at 6.41, 6.89 and 7.07 ppm representing the

protons at C4, C3 and C5 respectively (Figure 12). The coupling constant for those protons assigned at C3 and C4 was 3.85 Hz, which was characteristic of protons in the neighbouring C3/C4 environment upon a pyrrole ring.[82] Furthermore, the coupling constant between the proton at C3 and C5 was 1.62 Hz, which was characteristic of the *pseudo meta*-relationship on the pyrrole ring.[82] Considering the 3-substituted pyrrole **201**, there were three pyrrolic resonances at 6.49, 6.83 and 7.17 ppm representative of the protons at C4, C5 and C2 respectively. This assignment was supported by the small coupling constant between the protons at C2 and C4 of 1.60 Hz and the coupling between the protons at C4 and C5 of 2.80 Hz, both of which were consistent with the expected coupling constants in these environments.[82] Also, unlike that of the 2-substituted pyrrole **200** there was no coupling constant of an appropriate magnitude to suggest neighbouring protons at the C3- and C4-positions. Furthermore, ^{13}C NMR spectral analysis of the two compounds suggested that there was a pyrrolic carbon−iodine bond in the two compounds with the resonances at 96.7 ppm and 83.7 ppm for the 2-substituted pyrrole **200** and the 3-substituted pyrrole **201** respectively. Both the pyrrolic compounds had a 1,2-disubstituted benzene substituent that had a similar splitting pattern to the aromatic portion of both IBX (**197**) and the Dess−Martin periodinane (**165**), further supporting the incorporation of the reactant. The structural assignment was further supported with X-ray crystallographic evidence obtained from the 3-iodoniumpyrrole **201**, which clearly illustrated the incorporation of the IBX unit as a substituent on the pyrrole (Figure 13). The X-ray structure also gave categorical evidence to suggest that an iodine−carbon bond had formed at the C3-position of the pyrrole, with the classic T-shaped geometry around the iodine atom being observed. As with 2-iodoniumpyrrole **159**, that was observed under the PIFA (**131**) oxidation conditions, these two iodoniumpyrroles did not appear to be part of the oxidation pathway of 2-pyrrolinones when resubjected to the IBX oxidation reaction conditions.

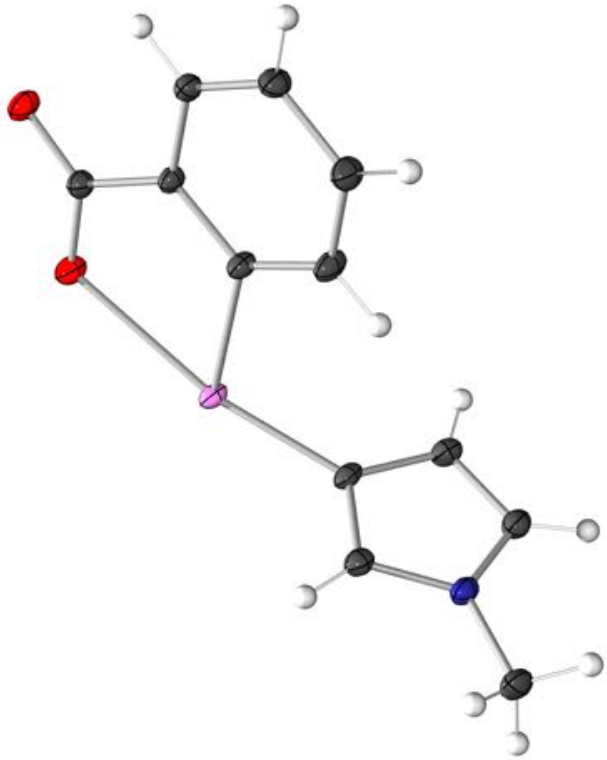
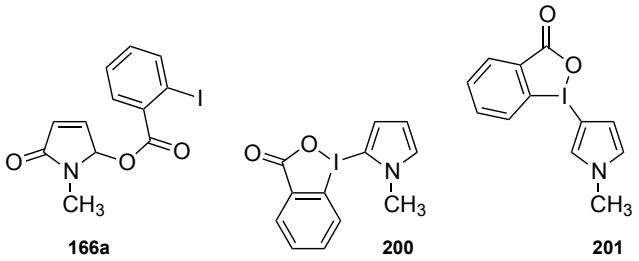


Figure 13: *X-ray crystal structure of the 3-iodoniumpyrrole* ***201*** *from IBX*

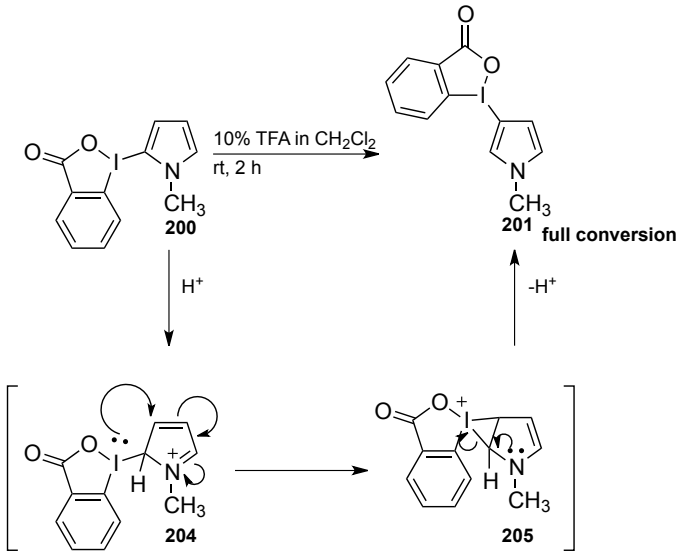
It was further found that the more water present resulted in a lowering of the yield of the crude reaction mixture, but increased the ratio of iodoniumpyrrole species to the 2-pyrrolinones (Table 3). This result was clearly demonstrated when the reaction was performed in 50% water/acetic acid, as the crude mixture was observed to consists of mostly iodoniumpyrrole species, with only a trace of the 2-pyrrolinones being observed. Furthermore, when the reaction was performed in neat TFA only 3-iodoniumpyrrole **201** was observed with no 2-pyrrolinone **166a** or **166b** or 2-idoniumpyrrole **200** being observed in the ^{1}H NMR spectrum.

Table 3: *Effect of H_2O on reaction mixture profile, as reported as ratios determined from the ^1H NMR of the crude reaction mixture*



% H_2O	2-Pyrrolinone 166a	2-Iodoniumpyrrole 200	3-Iodoniumpyrrole 201
5%	59%	30%	11%
10%	38%	44%	18%
15%	24%	52%	24%
20%	15%	59%	26%
50%	5%	56%	39%

While the production of 3-iodoniumpyrrole **201** was interesting, it was not initially obvious why it was produced under the reaction conditions, as substitution at the C3 position of pyrroles is uncommon and requires bulky *N*-substituents to force substitution away from the more nucleophilic C2 position. However, when the isolated 2-iodoniumpyrrole **200** was stirred for 2 h in 10% TFA/dichloromethane, a quantitative conversion to the 3-iodoniumpyrrole **201** was observed (Scheme 38). This observation suggested a rearrangement mechanism similar to that reported by Kakushima and Frenette and their work on the isomerisation of 2-alkythiopyrrole **202** to 3-alkylthiopyrrole **203** with TFA.[95]

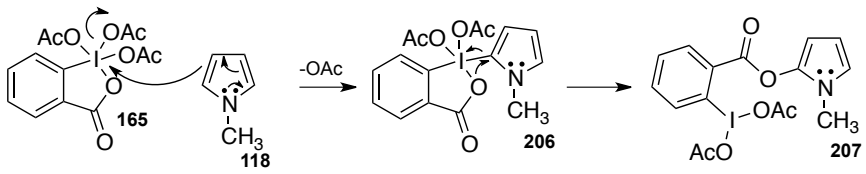


Scheme 38: *The acid-mediated rearrangement of the 2-iodoniumpyrrole* ***200*** *to the 3-iodoniumpyrrole* ***201***

The discovery of IBX substitution through iodine onto pyrrole was quite significant, and more so the isomerisation to the 3-iodoniumpyrrole **201**, as it was the first case of an isomerisation on pyrrole with an iodonium. It has been proposed that this molecule was perfectly set up for further cross-coupling chemistry, which could introduce a wide range of functionality at the C3 position of the pyrrole; a process, which is currently difficult on *N*-alkyl pyrroles. While using these iodoniumpyrroles as cross-coupling partners was not investigated during the course of the project, their discovery did lead to some interesting conclusions considering the reaction mechanism between both Dess−Martin periodinane and IBX with pyrroles.

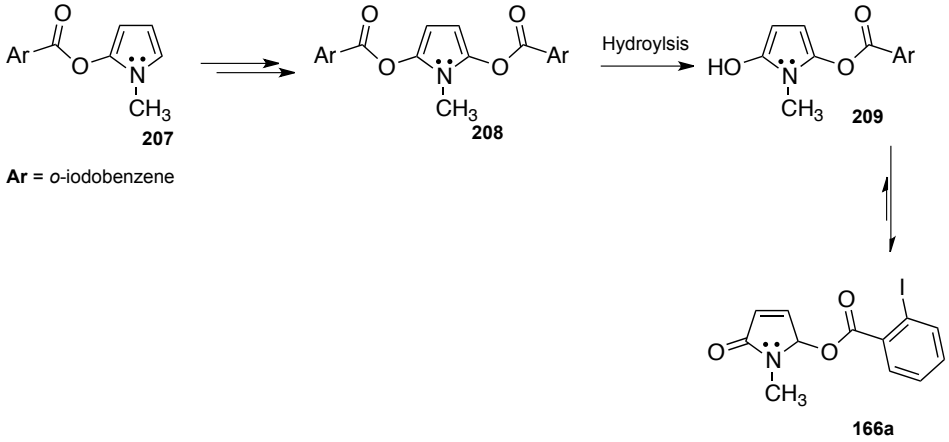
2.5 Mechanistic Considerations for the Controlled Oxidation of Pyrrole

A mechanism that could be proposed for the Dess−Martin periodinane oxidation of pyrrole resembles a similar mechanism proposed by Alp and co-workers (Scheme 19).[78] This involved an initial electrophilic aromatic substitution of the iodine atom of the Dess−Martin periodinane (**165**) onto pyrrole **118** (Scheme 39). Initially resulting in the C2 substituted iodoniumpyrrole **206**, a selective migration of the oxygen atom of the benzoate onto C2 of the pyrrole would result in **207**.



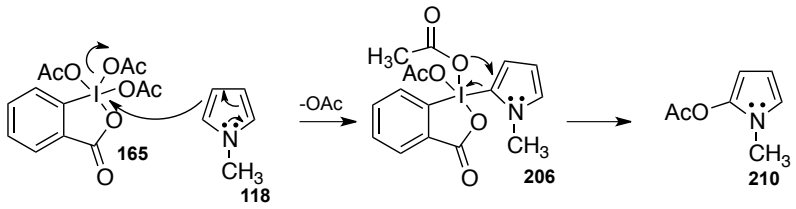
Scheme 39: *The initial electrophilic aromatic substitution step in the proposed oxidation mechanism*

Once formed, the intermediate **207** was more electron-rich and would likely be more reactive than the starting pyrrole **118** and a second substitution/migration takes place at the C5-position of the pyrrole ring, resulting in 2,5-diaroyloxypyrrole **208**. This intermediate would then be hydrolysed rapidly *in situ* to the reported 2-pyrrolinone **166a** (Scheme 40).



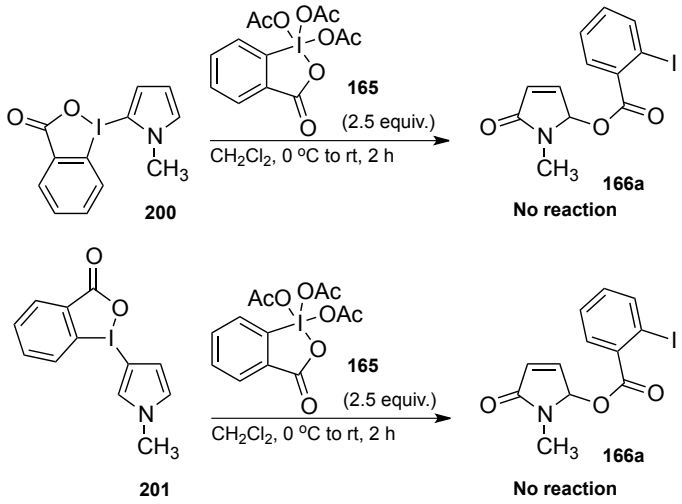
Scheme 40: *Once the mono-substituted pyrrole was formed, it was suggested the intermediate reacts rapidly with a second unit of Dess−Martin periodinane*

While no intermediates were observed in careful ^{1}H NMR based studies, this type of mechanism was not only supported by Alp and co-workers, but also partly supported by that proposed by Dess and Martin for their oxidation, where the first step was the electrophilic attack of an alcohol on the iodine.[89] The proposed mechanism for the Dess−Martin periodinane was plausible, however there were clear issues. The first one was that only trace amounts of the 5-acetoxy-2-pyrrolinone **166b** were ever observed, which was known to be produced from the reaction with acetic acid produced *in situ*. If the mechanism was to go through the proposed pathway, one would expect to observe an abundance of 5-acetoxy-2-pyrrolinone **166b**, as 1,2-migration of the acetoxy groups onto the ring would occur in competition with the migration of the benzoate group (Scheme 41).



Scheme 41: *The proposed mechanism for the formation of 5-acetoxy-2-pyrrolinone* ***166b*** *as an intermediate.*

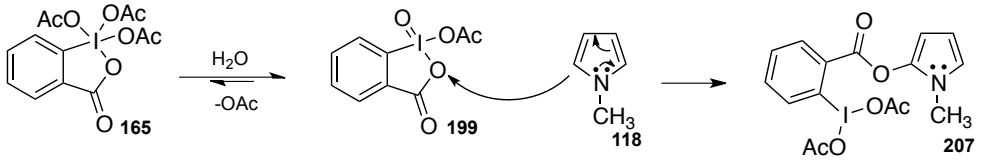
A second issue resulted from the two iodoniumpyrrole species isolated from the IBX reaction. Both 2-iodoniumpyyrole **200** and 3-iodoniumpyrrole **201** were subjected to the Dess−Martin periodinane oxidation conditions. It could be expected that the migration would occur from one of the pyrroles, however, neither reacted under the reaction conditions (Scheme 42). While this result was interesting, both of the iodoniumpyrroles were in the iodine (III) oxidation state, so it did not rule out the possibility that an iodoniumpyrrole at a higher oxidation state could be a reactive intermediate.



Scheme 42: *Results of treating iodoniumpyrroles with Dess−Martin periodinane*

Another point of interest concerns the enhanced reactivity of the reaction with water. As originally proposed by Meyer and Schreiber and further supported since by the work of Nicolaou, the acceleration of the Dess−Martin periodinane oxidation with water was due to the formation of the actual active oxidant on dissociation of an acetate group, which was aided by the additional water.[90,96-98] This oxidant has been proposed in the present thesis also and if it were to be the case the iodine would have increased electrophilic character. In theory, the actual active oxidant would react

faster towards pyrrole, however, it was still not clear why the proposed iodine/oxygen migration was strictly favoured towards the benzoate oxygen atom. It was possible then, that the iodine is drawing electron density away from the benzoate oxygen, making the oxygen electrophilic enough to directly participate in the electrophilic aromatic substitution of pyrrole (Scheme 43). With this mechanistic consideration in place, pyrrole can attack the benzoate oxygen and would lead to the same mono-benzoate species **207** as proposed earlier, before undergoing a second substitution to the 2,5-diaroxypyrrole **208**. It is also worth noting that this type of mechanism would also support the oxidation observed from the IBX/ acetic acid oxidation of *N*-methylpyrrole, as the active oxidant is proposed to be a partially acylated species from the acetic acid.



Scheme 43: *The potential for electrophilic oxygen participating directly in the oxidation of pyrrole*

It was clear that there was significantly more to the mechanism of the oxidation of electron-rich pyrroles with Dess−Martin periodinane (**165**) and IBX (**197**), and that it needs clarification with further study being required. It proved difficult to study due to the rapid reaction rates and the inability to observe reaction intermediates. In conclusion, the newly developed hypervalent iodine oxidation of electron-rich pyrroles remained with two potential mechanistic pathways. These were discussed as the electrophilic substitution of pyrrole onto the iodine of the oxidant followed by migration to oxygen, and the direct electrophilic oxygen transfer. The key to the mechanistic elucidation may however be in an advanced computational study.

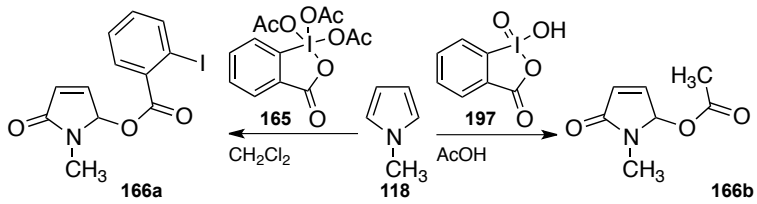
In summary, the validity of using hypervalent iodine reagents in the controlled oxidation of pyrroles has been further justified with the discovery of a new method for the controlled oxidation of electron rich pyrroles. PIFA (**131**) and PIDA (**141**) have been further investigated, and both Dess−Martin periodinane (**165**) and IBX (**197**) have been successfully shown to oxidise a range of pyrroles to 2-pyrrolinones. Significantly the oxidation of electron rich pyrroles has proceeded cleanly and with

limited decomposition or polymerisation, which is commonly not the case for pyrroles under oxidative conditions. The products of these oxidations are densely functionalised 2-pyrrolinones that contain a variety of synthetic handles to be exploited in the synthesis towards natural products and natural product inspired analogues. While these reactions were rapid and high yielding, there was a concern in the atom efficiency of the reaction. This concern is addressed in the following chapter.

Chapter 3 – Controlled Photo-oxidation of Pyrrole

3.1 Background

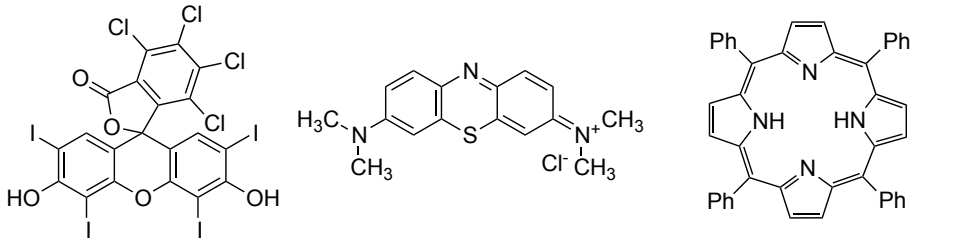
The previous chapter detailed the developments of the oxidation of electron-rich *N*-alkyl and *N*-aryl substituted pyrroles with the hypervalent iodine species Dess−Martin periodinane (**165**), producing 2-pyrrolinone products in high to excellent yields (Scheme 44). This exciting methodology was the first practical example of its kind and has proved to be convenient in constructing potential molecular scaffolds for further chemical manipulation towards pyrrolidine natural products and drug like molecules. While this was a valuable new method, we sought to find an alternative procedure that would avoid large masses of the oxidant, an exothermic workup and be able to oxidise a range of pyrroles, not just electron-rich systems.



Scheme 44: *Schematic summary of the controlled oxidations of pyrrole from Chapter 2*

While the aforementioned issues were not significant problems, different methods of successfully controlling the oxidation of pyrrole on a larger scale without the waste and potential hazard associated with using large amounts of oxidant were investigated. Many advances have been made in the methodology concerning the generation and use of singlet oxygen ($^1O_2$) for synthetic oxidations, so attention was turned to this oxidant as a practical starting point. The generation of $^1O_2$ comes from one of two routes: chemical decomposition of a densely oxygenated species, or the photoreaction with molecular oxygen (O_2). The photoreaction involving the excitation of the ground state of molecular oxygen, triplet oxygen ($^3O_2$), to the excited state, singlet oxygen ($^1O_2$), requires a dye sensitiser (typically Rose Bengal (**211**), methylene blue (**212**) or a porphyrin such as TPP (**213**) as illustrated in Figure 14).[99] This process involves the dye attaining its excited state after absorbance of light of an appropriate wavelength before transferring this energy to $^3O_2$, which

generates the higher energy singlet state of oxygen. Under suitable reaction conditions, due to the higher energy of the excited state, $^1O_2$ can then undergo various reactions with molecules that may typically not react with $^3O_2$, to generate a new oxygen containing molecule; this process is referred to as the chemical quenching mechanism.[99]



Rose Bengal (**211**) **Methylene Blue** (**212**) **Tetraphenylporphyrin** (**213**)

Figure 14: *Common sensitisers for the generation of $^1O_2$*

Dye-sensitised photo-oxidation has been utilised broadly in organic synthesis allowing access to a range of oxidised compounds.[100,101] Once generated, $^1O_2$ can react as a dieneophile in a Diels-Alder [4+2]-cycloaddition, participate in [2+2]-cycloadditions or facilitate an ene reaction (Figure 15).

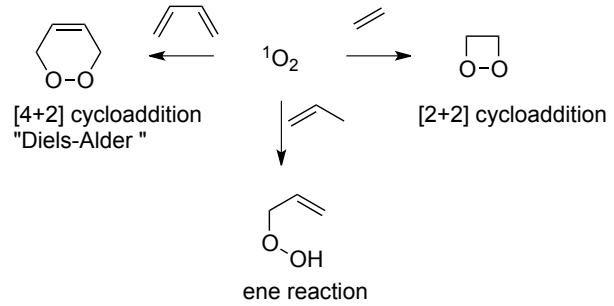


Figure 15: *Generalised examples of organic reactions involving $^1O_2$*

More specifically, $^1O_2$ has been used in the oxidation of heterocycles including various furans, oxazoles, imidazoles and even pyrrolic species, among others. While these oxidations often lead to good conversions of the desired products in most heterocyclic systems, pyrrole is often reported as producing low yields of the desired pyrrolinone with large amounts of undesirable “tarry products” existing as by-products.[58]

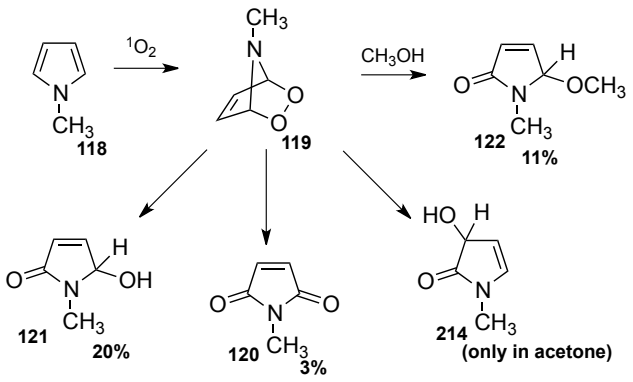
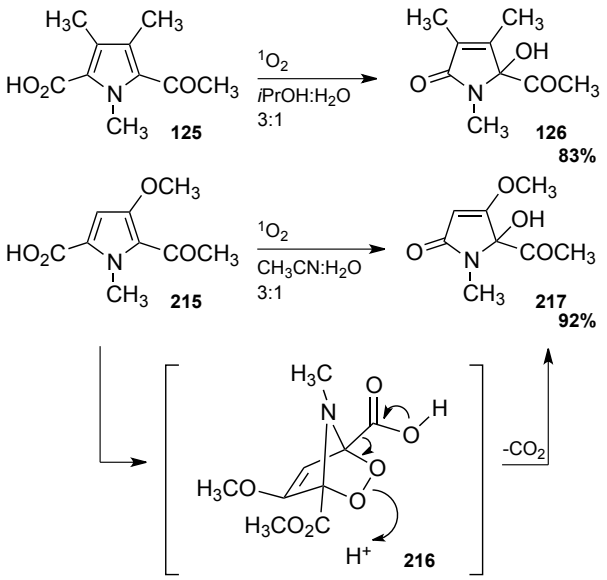


Figure 16: *The diversity of pyrrolinone products as found from the reaction of N-methylpyrrole with $^1O_2$, as according to Lightner and co-workers*

While the oxidation of pyrrole has been extensively studied for its array of potential products and its mechanism (Figure 16), the yield of the products has often remained low, limiting its synthetic utility (usually sub 40% yield for a mixture of products).[65,68] An exception to this was the photo-decarboxylation reactions preformed by the research groups of Boger and Wasserman and their colleagues which gave good to excellent yields for a number of specific pyrrolic species (Scheme 45).[69-71] The generation of 2-pyrrolinone in this case was a result of decarboxylation post $^1O_2$ addition to the pyrrole ring and, while excellent chemistry, demanded specific starting materials (**125** and **215**). Interestingly, Boger coupled a uranium yellow glass filter with the white light source that allowed light to only transmit at wavelengths greater than 330 nm, limiting the UV transmittance further than the ~300 nm filter that was found from traditional borosilicate laboratory glassware.[102] The use of a filter was not a common practice taken in photo-oxidations, especially those involving pyrrole, and as such it was perceived that the low yields commonly associated with photo-oxidation was a result of poor experimental design, rather than a result of pyrrole being difficult to oxidise.



Scheme 45: *The photo-oxidation of pyrrole performed by the groups of Boger and Wasserman*

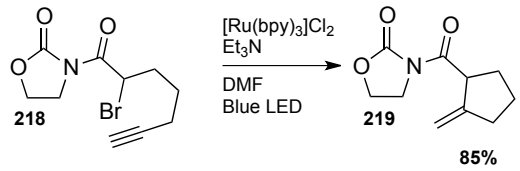
The filtering of unwanted wavelengths may aid in a higher yield of the desired products in reducing the yield of unwanted polymerisation, which may partially occur due to exposure from UV light. Commonly, a high intensity broadband light source was used in the generation of $^1O_2$ such as high-pressure Hg lamps and halogen lamps, which both emit UV light. Pyrrole is a strong absorber in the UV region, and when exposed to shorter wavelengths pyrrole attains its own excited state, which can lead to the polymerization and the production of the previously mentioned "tarry products", which is known as polypyrrole or pyrrole black. In contrast, pyrrole does not absorb visible light and will not polymerise when exposed to only visible light.[103,104]

The dyes commonly used for photosensitising consist of a single dominant absorbance band that is responsible for a particular colour observed (Rose Bengal (**211**) is red/pink, while methylene blue (**212**) is blue). As such, the dye can be exposed to a narrow spectral band of light of the reciprocal colour of the dye, which in turn can generate the excited state of the dye. Furthermore, if the light source chosen has a narrow emission spectral band then selective excitation of the dye sensitiser, in the presence of other molecules, was likely possible. It was conceivable then that if the light source chosen emits in a narrow wavelength range or it was

restricted selectively and only excited the dye and no other molecules then controlled oxidation of pyrrole is possible in high yields.

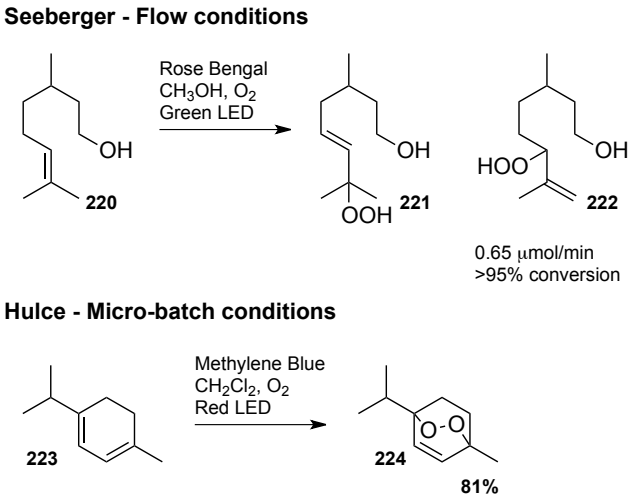
As determined, one way to produce a wavelength-specific light source in a synthetic reaction was with a light filter. However, this route was deemed as impractical due to the limited availability of custom glass filters in a standard laboratory and the cost associated with making custom glassware. The other way to achieve a selected light source was to use a source that only emitted light in a narrow wavelength range. This technology is available in the form of lasers and LEDs. Lasers offer a significantly narrower wavelength range than that of LEDs, however, the cost associated with lasers was high and designing a practical system that incorporated a laser or lasers appeared cumbersome. In contrast, LEDs offered a cheap alternatives to lasers, were easily obtained in many different colours, were available in multiple forms such as a single bulb or in flexible strips making them amenable to reactor designs and can run at low power, further reducing running costs.

The principal of using a selective light source, such as LEDs, to activate a photo-catalyst or dye sensitiser has gained much attention in the recent literature. As a highlight, the research developed within the Stephenson group has focused heavily on the activation of catalysts with white light, with a direction towards activating the same catalysts with the appropriate selective wavelengths.[105] As a selected example of their recent work, they have demonstrated the radical cyclisation of a range of substrates in the presence of the $[Ru(bpy)_3]Cl_2$ and blue LEDs (Scheme 46).[106] Blue LEDs emit light with a local maxima at 435 nm, while $[Ru(bpy)_3]Cl_2$ absorbs light strongly at 425 nm, which made the LED/catalyst system a good match. By using the blue LEDs over a traditional white light source, an observation of an accelerated reaction rate was reported for the radical 5-*exo-dig* cyclisation. Stephenson's group has experimented with both batch LED reactors and flow reactor systems.



Scheme 46: *Stephenson's radical cyclisation with blue LEDs*

Dye-sensitised photo-oxidations have only employed LEDs in a few limited studies. While batch reactors have largely been ignored, there are some interesting cases involving flow systems. For example, research within the Seeberger group, has focused on using Rose Bengal (**211**) and TPP (**213**) as dye sensitisers to oxidise a range of organic molecules in continuous flow reactors.[107] The approach used was to pump the reaction mixture, saturated with O_2, through a silicon-glass microreactor exposed to a LED light source (Scheme 47). This system provided an excellent conversion for the well-known photo-oxidation of citronellol (**220**) in an optimised productivity of 0.65 μmol/min. However, for larger flow systems Seeberger and co-workers returned to traditional Hg high-pressure lamps as the light source. In contrast to batch oxidations, "micro-batch" photo-oxidations utilising LEDs has been successfully shown. For example, Hulce and co-workers have nicely demonstrated the use of LEDs in the controlled photo-oxidations on a range of substrates (Scheme 47).[108] They demonstrate efficient conversions to oxidised products, reacting precise amounts of $^1O_2$ with low concentrations of starting materials utilising methylene blue (**212**) as their dye-sensitiser with red LEDs. This was demonstrated in a closed vial with three individual LEDs focused onto the vial. These two examples excellently demonstrate the applicability of LEDs to photo-oxidation systems, with both examples showing comparable or significantly better results to using a conventional light source. However, both examples demonstrate using LEDs on only micro systems, which leaves a need for the development of larger scale photo-reactors utilising LEDs.



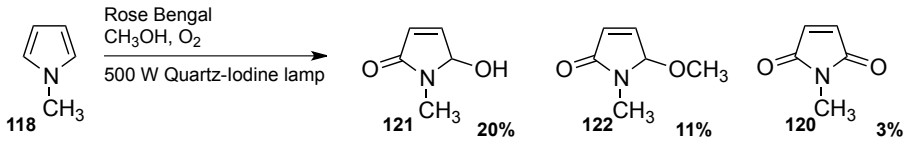
Scheme 47: *Seeberger and co-workers flow conditions for the photo-oxidation of citronellol with green LEDs and Hulce and co-workers photo-oxidation of α-terpinene with red LEDs.*

As discussed, LEDs are a selective source of visible light that can be utilised for synthetic applications, however for LEDs to be exploited in a photo-oxidation system, the starting materials and the products of the oxidation need to be transparent to the wavelength emission of the LEDs. With pyrrole being a strong absorber only in the UV region, it was postulated that LEDs would be ideal for the photo-oxidation of pyrroles by singlet oxygen. Designing a batch photo-reactor with the aim of oxidising pyrrole without generating unwanted by-products by only targeting the photo-sensitiser would address two gaps in the literature: the lack of a batch LED photo-reactor; and improving upon the poor yields commonly observed with pyrrole photo-oxidation.

3.2 Photo-oxidation of pyrrolic species with LED photo-reactor

The photo-oxidation of pyrrole to 2-pyrrolidinones was, as previously discussed, a low-yielding reaction, with the loss of yield attributed to the production of the by-product polypyrrole. It was reasoned that this was due to traditional methods of photo-oxidation utilising broad-spectrum light sources with UV emissions. With literature precedence,[107,108] LEDs were postulated to allow for the successful oxidation of pyrrole to 2-pyrrolidiones without the production of unwanted by-products. Further to this, the photo-oxidation of pyrrole would ideally be on a larger scale than those LED photo-oxidation examples within the literature. Thus, the following account details both the design and development of an LED batch photo-

oxidation reactor, and the oxidation of pyrrolic species under the conditions provided by the reactor.



Scheme 48: *Lightner and co-workers photo-oxidation of N-methylpyrrole, which was used as a comparative standard*

With an aim to directly compare results to the well-established literature methods it was initially decided to use Rose Bengal (**211**) as the dye photo-sensitiser with an alcohol as the solvent (Scheme 48).[64,65] Rose Bengal was documented to have an absorbance local-maxima (λ_{max}) at 559 nm in ethanol, which is located in the green region of visible light.[109] This literature data, matching that obtained experimentally, meant that a green light (in the form of cheap, low power consuming, green LEDs) was needed to excite the dye. The emission of readily available green LED strips was measured and found to have a λ_{max} at 517 nm (with an emission of light only occurring between approximately 450 nm and 600 nm). While not perfectly aligned with Rose Bengal, the emission band of the green LEDs overlapped the absorbance band of the dye, and more importantly had no transmittance into the remainder of the UV-Vis spectrum (Figure 17). In a quick qualitative test, a 532 nm green laser was shone into a vial containing a solution of Rose Bengal in ethanol. It was observed that the light penetrated through the glass wall of the vial, however was absorbed by the solution and did not exit the vial, indicating proof of principal.

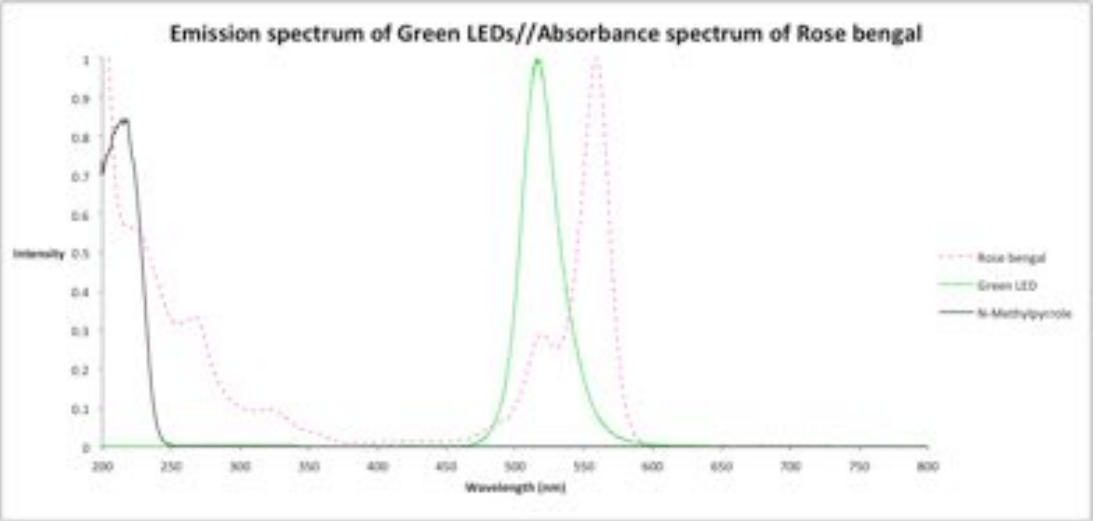


Figure 17: *Emission Spectrum of green LEDs vs. the absorbance spectrum of Rose bengal and N-methylpyrrole*

A wide range of LEDs types are available on the market, yet as the desire was to keep the design cheap, general and convenient, common green LED flexible strips in 5 m coils were sourced. The LED strips were waterproof, contained 120 individual 3.5 mm x 2.8 mm LEDs per metre and had an output, or radiant flux, of 4.8 W/m (Figure 18). The LED strips could be cut to a custom length and only required a 12 V power source to operate, which further lowered the cost associated with the system due to the low power requirements. Other common LED strips contain larger individual LEDs, which, while offering more radiant flux per LED in comparison to the smaller LEDs, the density of LEDs along the strip has to be comparatively lower, resulting in a lower radiant flux along the entire strip.

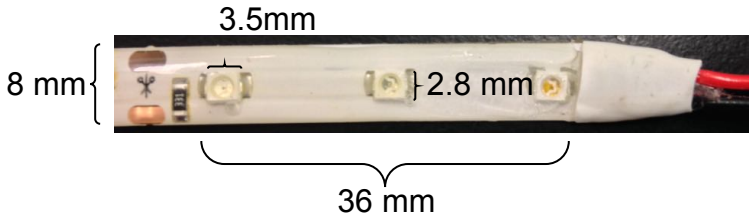


Figure 18: *Close-up examination of the dimensions of the green LED strip*

Conventionally, when a photo-oxidation was performed the light source was either contained within the reaction vessel in a cooled immersion well or located outside of the reaction vessel and focused into the vessel. Due to the intensity of the light sources used in typical photoreactions, a large concentration of radiant flux was

provided to the reaction vessel with a trade off existing in increased temperatures, which was not ideal for some chemical reactions. A convenient coincidence of using LEDs was that the temperature did not increase greatly when the power was on, and as such LEDs can be used on contact with the reaction vessel. With this technical allowance, the LEDs strips could be wrapped around the outside of a reaction vessel, pointing into the vessel without greatly increasing the temperature of the reaction flask. This design choice was justified in ensuring the maximum radiant flux was present inside the reaction vessel, rather than lost due to dispersion if the LEDs were suspended outside the flask. This concept of ensuring maximum radiant flux would likely be similar if the LEDs were placed inside the reaction vessel, however, once light had exited the reaction vessel it would be lost, instead of the added reflections found from focusing the LEDs into the vessel. As such, a conscious decision was made to construct a photo-oxidation reactor where the green LED strip was cut to an appropriate length and wrapped around the surface of a glass vessel, focusing the light into the vessel.

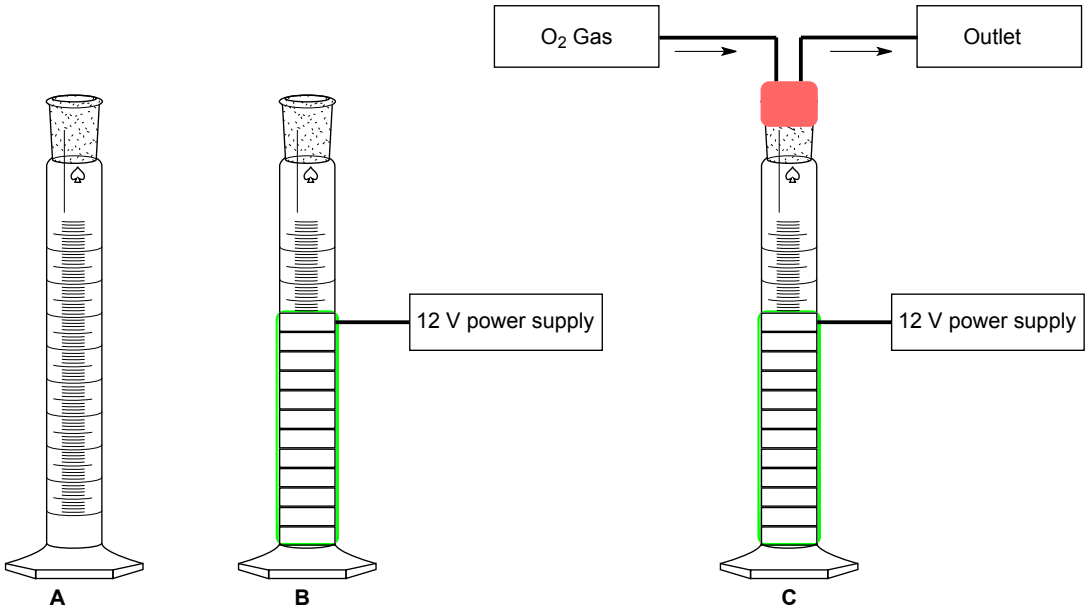


Figure 19: *Schematic of the design of the proposed photo-reactor to be utilised for photo-oxidations.* ***A****. A standard 100 mL measuring cylinder.* ***B****. The green LED strip wrapped around the 100 mL cylinder connected to a 12 V power supply.* ***C****.* O_2 *gas introduced to the photo-reactor.*

Simplicity and convenience continued to stay in the forefront of planning in considering the dimensions of the glass vessel to be used for the photo-oxidation

reactor. Custom pieces and glassware were avoided and only glassware found within a standard synthetic chemistry laboratory were considered for use. The vessels volume was restricted to 100 mL, as a volume of this magnitude offered and appropriate trial of the photo-oxidation reactor without the waste of materials and solvents that may be associated with larger systems. Addressing these considerations, a 100 mL graduated measuring cylinder was chosen as the photo-oxidation reactor (Figure 19 - **A**). A cylindrical piece of glassware was chosen over a conventional round bottom flask as the cylinder offers a great surface area to volume ratio than a sphere, which allowed for a greater density of LEDs to be attached to the surface of the glassware.[§] Thus, an LED strip was cut to length and attached to the surface of a 100 mL measuring cylinder with adhesive tape in a tight spiral from the bottom of the cylinder to the 70 mL graduation (Figure 19 - **B**). This length was measured at 85 cm and contained 102 individual LEDs, providing approximately 4.08 W of radiant flux to the system.

The reactor design described above provided the necessary vessel to contain the reaction mixture and provide the light in a cheap, simple and convenient way as required. However, there was still a need to introduce oxygen to the system to generate the necessary conditions for the sensitised photo-oxidation methodology to be successful. A solution to this was to attach a rubber septum to the top of the measuring cylinder and then thread two needles into the septum (Figure 19 - **C**). One needle submerged into the reaction mixture as an oxygen inlet, while the second needle only inhabited the headspace of the reactor and acted as an outlet to prevent excessive pressurisation of the reactor. The design allowed for the inlet needle to be attached, by Tygon® flexible tubing, to a pressurised oxygen gas cylinder *via* the regulator, thus introducing oxygen gas to the system at a controllable flow rate. With the discussed design considerations in place, a photo-oxidation reactor was constructed to begin the oxidation trials on pyrrole (Figure 20).

[§] This can be calculated as a surface area of ~169 cm^2 for a 100 mL measuring cylinder with a radius of 1.5 cm and a height of 18 cm, and ~113 cm^2 for a 100 mL spherical round bottom flask with a radius of 3 cm.

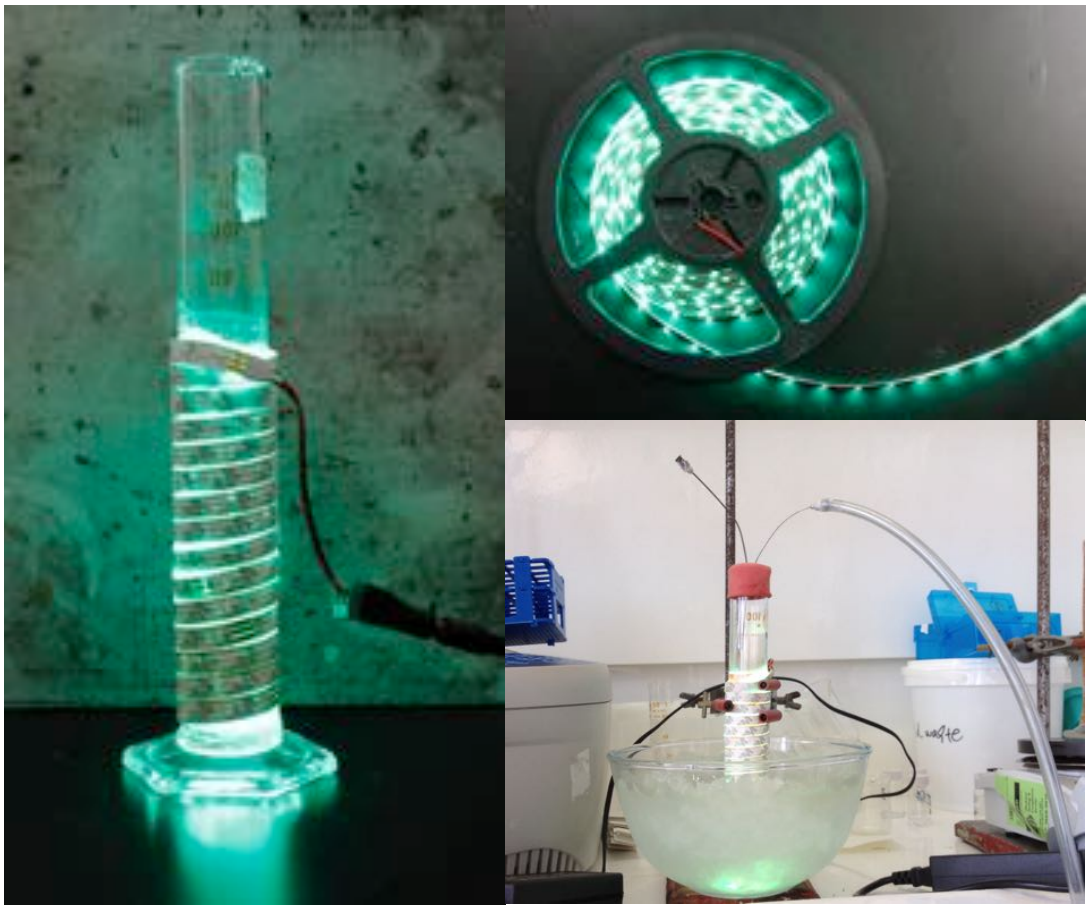
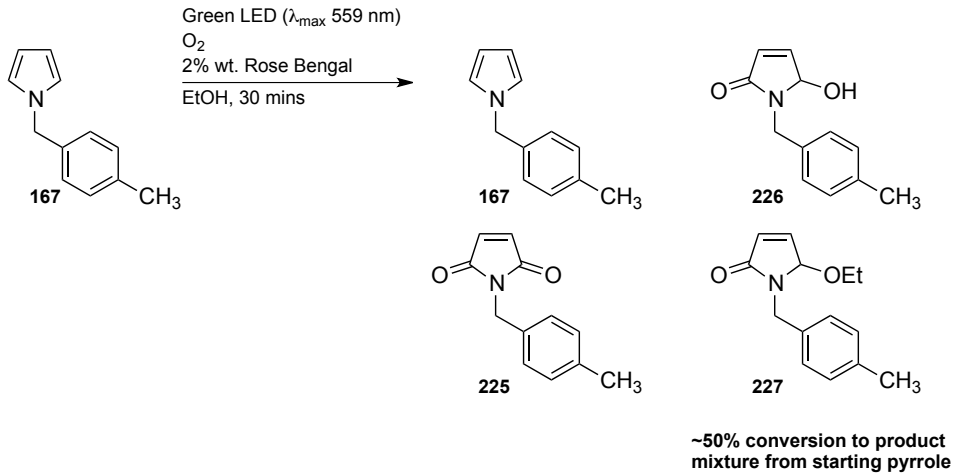


Figure 20: *Photos displaying the photo-reactor used during this study*

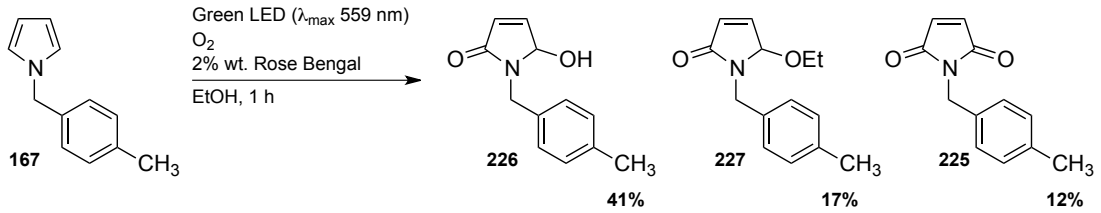
Initial reactions and optimisation were performed with *N*-(4-methylbenzyl)pyrrole (**167**) due to its higher boiling point in relation to both pyrrole (**81**) and *N*-methylpyrrole (**118**), which would both be lost due to evaporation on workup and limit the credibility of the observed reaction conversion. The photo-reactor was loaded with a solution of approximately 200 mg of *N*-(4-methylbenzyl)pyrrole (**167**) in ethanol with 2% wt/wt Rose Bengal (**211**). This amount of pyrrole was chosen as it gave a molar concentration that was comparable to Lightner and co-workers experiments.[64, 65] The reactor was run with a steady stream of O_2 bubbling through the solution for 30 min, which by analysis of the ^{1}H NMR spectrum of the crude reaction mixture contained a mixture of four compounds; the starting pyrrole **167**, *N*-(4-methylbenzyl)maleimide (**225**), the related 5-hydroxypyrrolinone **226** and 5-ethoxypyrrolinone **227** in an approximately 1:1 ratio of starting material to product (Scheme 49).



Scheme 49: *Initial photo-oxidation reaction of N-(4-methylbenzyl)pyrrole using the LED photo-reactor*

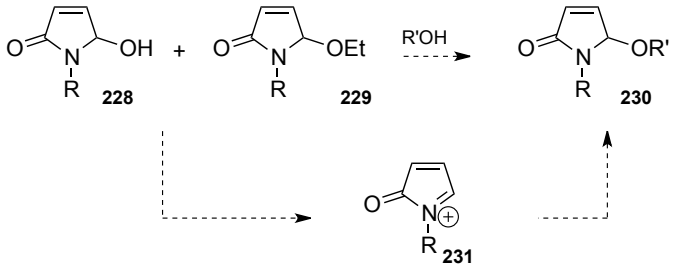
Longer reaction times were predictably found to consume more of the starting material. The reaction was found to run to completion at room temperature over 1 h, however, there was a notable loss in recovered mass at this temperature, likely due to decomposition. Due to the LEDs not generating a large amount of heat while in operation, heat was not a significant issue for the reaction. However, it was considered that if it were possible to cool the reactor below room temperature, decomposition from longer reaction times would be reduced. As the LEDs were waterproof the reactor could be operated comfortably in an ice bath to allow the reactor to be run at approximately 0 °C (Figure 20). Due to the potential safety concerns with using pure O_2 gas, a stream of air was tested in the reaction. While the reaction still went to completion, the reaction had to be run for 2 h due to the diluted concentration of O_2 now provided to the system. It was deemed impractical to run the system longer than was required due to the potential of decomposition of the products so pure O_2 gas was kept as the pre-oxidant system, rather than air.

The oxidation of *N*-(4-methylbenzyl)pyrrole was performed in the photo-reactor for 1 h in an ice bath and with O_2 gas bubbling through the solution. The oxidation successfully went to completion, consuming all of the starting pyrrole to produce *N*-(4-methylbenzyl)maleimide (**225**) in a 12% yield, 5-hydroxypyrrolinone **226** in a 41% yield and 5-ethoxypyrrolinone **227** in a 17% yield after flash chromatography on silica gel (Scheme 50).



Scheme 50: *Isolated yields of products from the photo-oxidation of N-(4-methylbenzyl)pyrrole after 1 h*

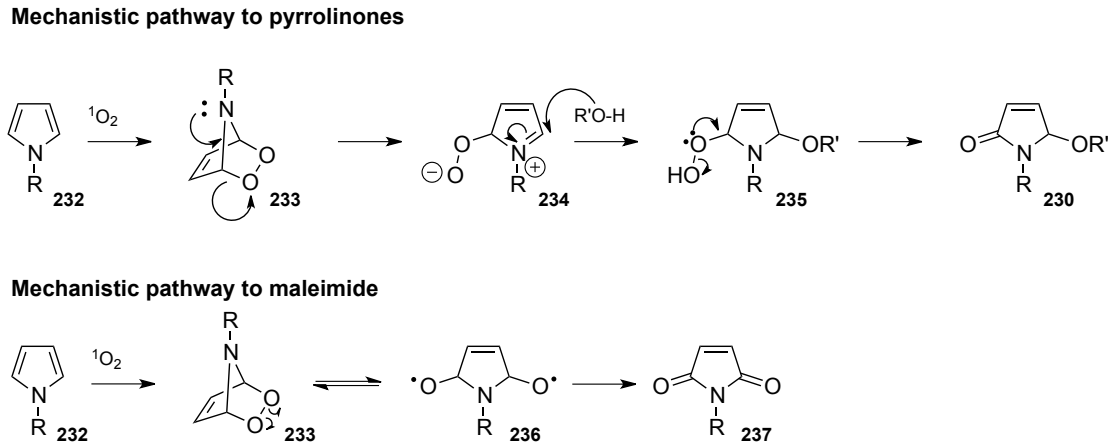
While a mixture of products is generally unfavourable, the resulting hydroxy- and the ethoxy-pyrrolinones (**228** and **229**) would react in the same way under reaction conditions that gave an *N*-acyliminium ion intermediate (**231**). However, if it was important to only form one pyrrolinone, it was conceivable that either species could be converted from one to the other. This could be achieved by either acid hydrolysis of the ether **229** to the hydroxyl-pyrrolinone **228** or by generating the common *N*-acyliminium ion intermediate **231** from the mixture and then capturing it with ethanol to form the 5-ethoxy-2-pyrrolinone **230** (Scheme 51). The major problem was in the production of the maleimide (**237**), which was a dead-end product, hindered purification and lowered the effective yield of the reaction.



Scheme 51: *The concept behind generating a single compound from the mixture of pyrrolinones*

To limit the production of maleimide it was postulated that introducing an external acid or base could act to open the intermediate endoperoxide ring before it decomposes to the maleimide. This postulate seemed reasonable from the proposed mechanisms presented by both Lightner and Alberti and it has been shown that that 2-pyrrolinones **228** and **229** are not precursors to the maleimide by-product (Scheme 52).[65,68] After the addition of singlet oxygen to pyrrole, an unstable endoperoxide **233** intermediate was formed and can be directly opened by a nucleophile to result in a 2-pyrrolinone (**230**). The alcohol solvent or water can both act as weak nucleophiles to directly open the endoperoxide, however, it was likely that the

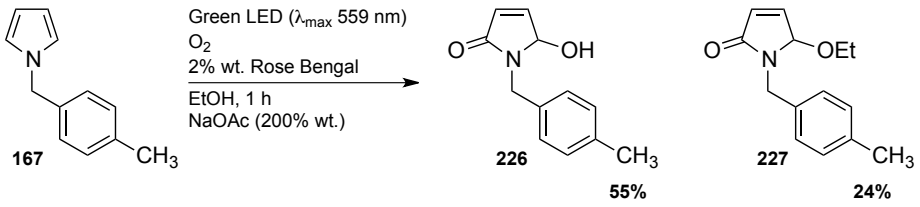
endoperoxide rearranges to *N*-acyliminium ion **234** and was captured by the nucleophile at that stage. The maleimide **237** was possibly the result of a competing mechanistic pathway where the endoperoxide was in equilibrium with diradical **236**, which can directly produce the maleimide.[65,68,110] Considering these two pathways, it was conceivable to be able to limit the production of the maleimide by biasing the 2-pyrrolinone pathways. Thus, a nucleophilic additive could assist in opening endoperoxide **233** or capture the *N*-acyliminium ion **234** faster than the maleimide production. A base additive could be used to either directly act as a nucleophile in this way or act as a base and deprotonate the solvent, generating the strong alkoxide nucleophile *in situ*. An acid on the other hand would provide a convenient proton source to protonate nitrogen before opening the endoperoxide to directly produce the hyroxypyrrolinone. However, acids were ruled out quickly due to the pH sensitivity of Rose Bengal (**211**) (in an acidic environment Rose Bengal becomes colourless, and shuts down the production of $^1O_2$).



Scheme 52: *The proposed mechanism for pyrrole photo-oxidation from both Lightner and Alberti*

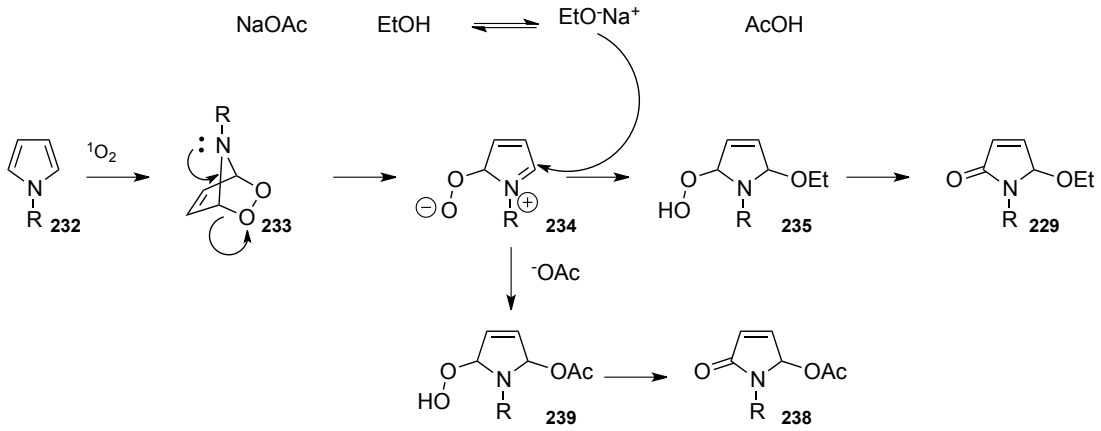
Revisiting earlier literature, a single comment was found in Lightners 1975 paper that stated that the presence of ammonia in the photo-oxidation prevented the formation of maleimide from the product mixture.[64] Thus, the addition of ammonia to the reaction was tested by performing the oxidation with 1% (v/v) ammonia solution in the reaction mixture (600 μL in 60 mL of ethanol). While this did indeed limit the formation of the maleimide, as seen by the near disappearance of the singlet at 7.09 ppm in the ^{1}H NMR of the crude reaction mixture, the reaction was much lower yielding. This was also found to be the case for other bases, including solid

and aqueous NaOH and KOH, solid and aqueous K_2CO_3 and even from the *in situ* generation of NaOEt with Na metal. However, gratifyingly it was found that upon the addition of solid NaOAc, maleimide production was greatly reduced without affecting the yield. NaOAc was not very soluble in ethanol and was an issue that led to inconsistent yields, so a saturated solution of aqueous NaOAc was added to the reaction mixture that gave consistent high yields without the production of maleimide (200 μL of saturated aqueous NaOAc in 60 mL EtOH). Thus, under these new optimal conditions, the oxidation of *N*-(4-methylbenzyl)pyrrole (**167**) produced 5-hydroxypyrrolinone **226** in a 54% yield and 5-ethoxypyrrolinone **227** in a 24% yield (Scheme 53).



Scheme 53: *Isolated yields of products from the photo-oxidation of N-(4-methylbenzyl)pyrrole after 1 h with NaOAc as an additive in the reaction mixture*

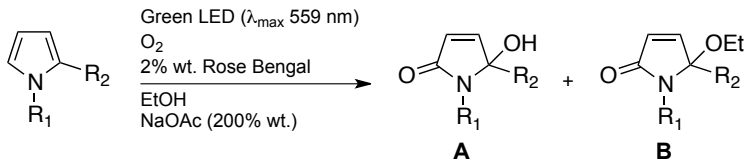
As a result of using NaOAc in the photo-oxidation, trace amounts of the 5-acetoxyl-2-pyrrolinone **238** was observed in all reactions (Scheme 54). This was likely a result of either the acetate reacting directly on the enodperoxide or the *N*-acyliminium ion, rather than exchange for the ether on the 2-pyrrolinone post reaction. However, it was again conceivable that the 5-acetoxypyrrolinone would react to produce the common *N*-acyliminium ion intermediate just as the ethoxy- and hydroxyl-pyrrolinones, and as such was of no concern as it was not a dead-end product.

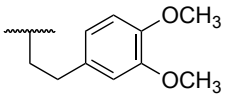


Scheme 54: *Mechanistic justification for the use of sodium acetate*

On a 200−500 mg scale, the optimised photo-oxidation conditions with green LEDs for *N*-(4-methylbenzyl)pyrrole (**167**) gave consistent yields of approximately 55% and 24% of the 5-hydroxy-2-pyrrolinone **226** and 5-ethoxy-2-pyrrolinone **227** respectively. This methodology was applied to a range of pyrroles as summarised in the table below (Table 4). Of immediate note was the oxidation of *N*-methylpyrrole (**118**) that gave a combined product yield of 61% of 2-pyrrolinones (Table 4 - Entry **1**), which was excellent in comparison to Lightner's research where a 31% yield of the product mixture was reported. Pyrrole itself gave a moderate yield of only the alkyl ether product **240** in 48% (Table 4 - Entry **6**), which was a significant result due to pyrrole's propensity towards polymerisation. The incorporation of an electron withdrawing sulfonyl group on the nitrogen had no effect on the photo-oxidation (Table 4 - Entries **8** & **9**), which was in contrast to the Dess−Martin periodinane oxidations; however, these reactions did not proceed as cleanly as the *N*-alkyl pyrroles. Unlike the Dess−Martin periodinane oxidation of pyrroles with C2 substitution, no elimination product was observed from the photo-oxidation reactions presumably due to alkaline conditions found in the photo-oxidation conditions compared to the acidic environment of the hypervalent iodine chemistry (Table 4 - Entries **7** & **9**). Larger scale reactions were attempted with up to 2 g of *N*-methylpyrrole (**118**) in a 200 mL green LED reactor to keep the concentration of pyrrole similar. These reactions proceeded, however, gave significantly reduced yields. It was found that the methodology could comfortably support reactions up to ~500 mg without reduction of the yield.

Table 4: *Photo-oxidation of a range of pyrroles.*



Entry	Pyrrole	R^1	R^2	Yield of A	Yield of B	Combined Yield
1	**118**	-CH_3	-H	48%	13%	61%
2	**173**	-*p*-C_6H_4-OCH_3	-H	21%	9%	30%
3	**167**	-CH_2-(*p*-C_6H_4-CH_3)	-H	54%	24%	78%
4	**175**		-H	34%	20%	54%
5	**241**	-$(CH_2)_3$-CO_2CH_3	-H	34%	23%	57%
6	**81**	-H	-H	-	48%	48%
7	**190**	-CH_3	-C_9H_{19}	35%	22%	57%
8	**108**	-Ts	-H	30%	trace	30%
9	**242**	-Ts	-Bn	-	33%	33%

Other light sources were also investigated to see if there was an enhanced yield from different energetic wavelengths or dyes. As with Rose Bengal (**211**), the absorbance spectra for methylene blue (**212**) and TPP (**213**) were measured to assess an appropriate light source to excite them. It was found that methylene blue (**212**) had a local λ_{max} of 655 nm, which approximately matched the light emissions of red LEDs at 632 nm, while TPP (**213**) had a local λ_{max} of 413 nm, just overlapping the emission from blue LEDs at 452 nm (Figure 21). As such each dye was used with its appropriate light source to oxidise *N*-(4-methylbenzyl)pyrrole (**167**) in dichloromethane. Moving away from using ethanol as the solvent of the photo-oxidation and using dichloromethane was ideal, as it would likely only produce a

single product, the hydroxyl species. Using dichloromethane in the green LED/Rose Bengal system was not possible due to the lack of solubility of Rose Bengal in dichloromethane. However, the oxidation in these modified systems did not produce comparable yields of 2-pyrrolinones and were found to be generally unreliable by not readily going to completion or producing a complex mixture with low mass recovery in the photo-oxidation of *N*-(4-methylbenzyl)pyrrole (**167**). As such, the use of different dyes and light sources were not pursued further for the oxidation of pyrrole.

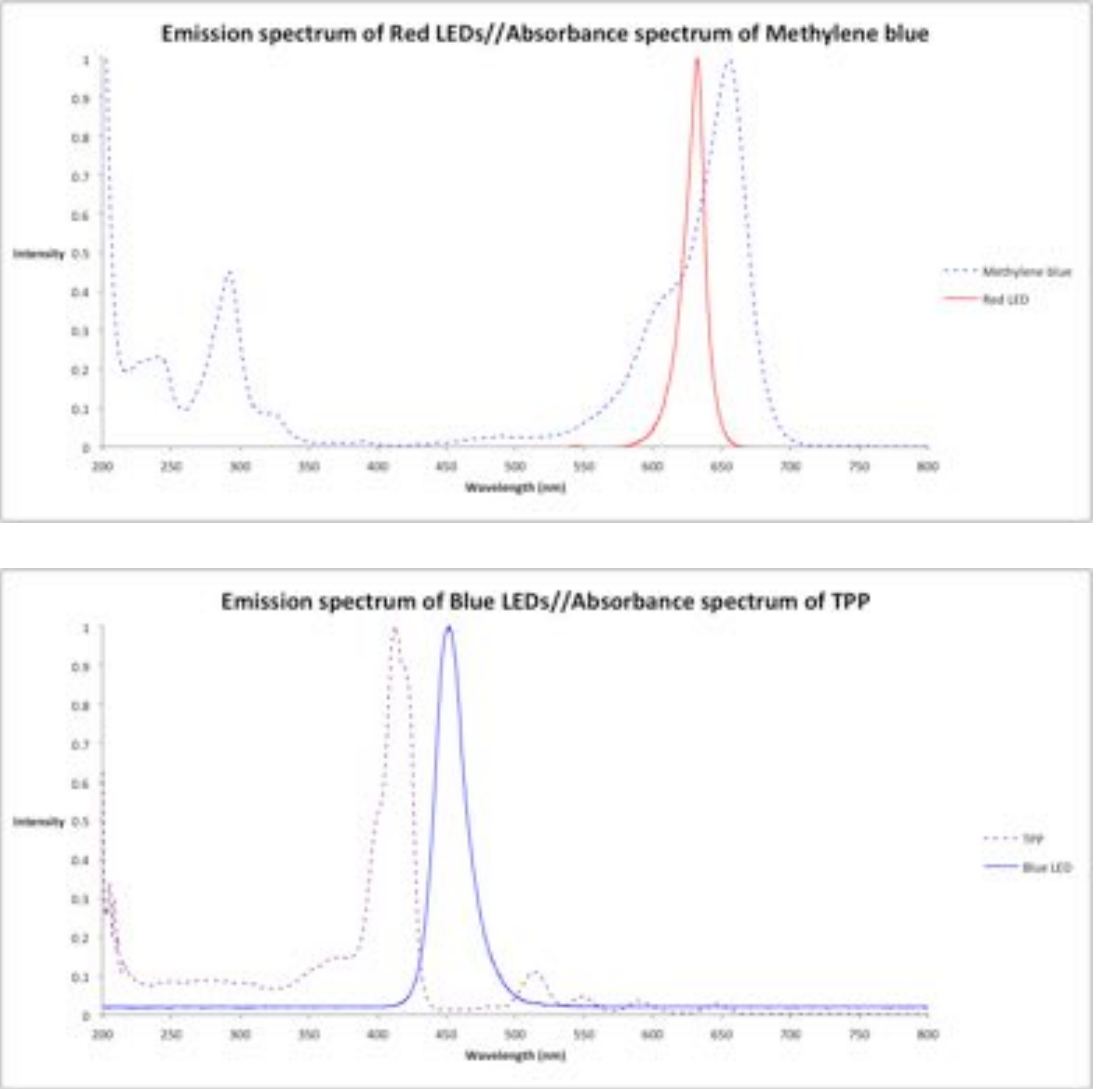
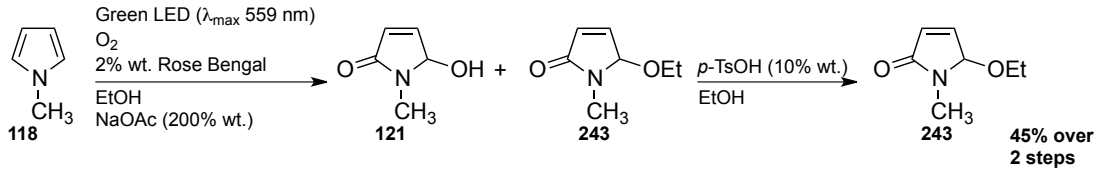


Figure 21: *Emission spectra for both red LEDs and blue LEDs vs. the absorbance spectra of methylene blue and TPP*

As support for the proof-of-concept that the pyrrole photo-oxidation methodology was practical, *N*-methylpyrrole (**118**) was oxidised under the optimised conditions followed by transforming the reaction mixture into a single compound (Scheme 55).

This was achieved by treating the reaction mixture with an acid to generate the *N*-acyliminium ion *in situ* that was captured by a nucleophile. In ethanol, *p*-TsOH was used as the acid catalyst at room temperature over 4 h to produce the ethyl ether **243** in a 45% yield over 2 steps from the *N*-methylpyrrole (**118**).

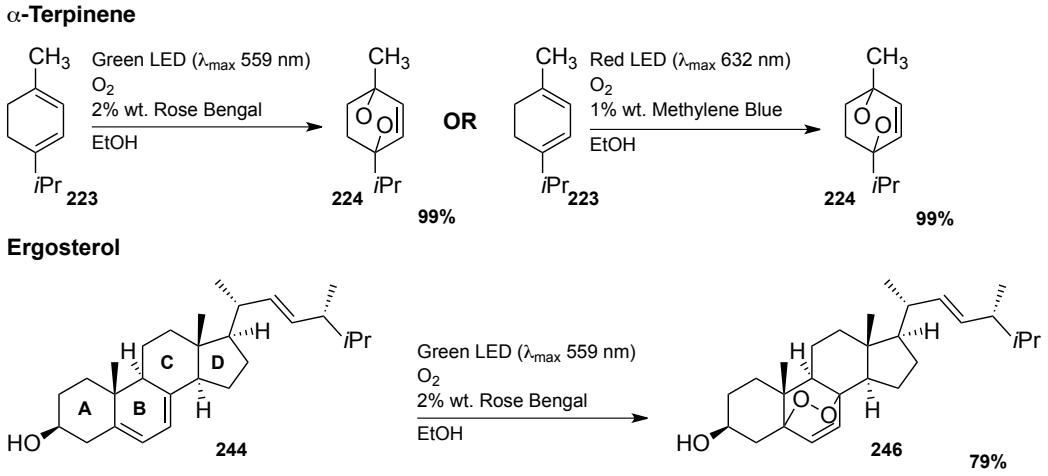


Scheme 55: *Post oxidation modifications to the 2-pyrrolinone products*

3.3 Other oxidations to demonstrate general batch capability.

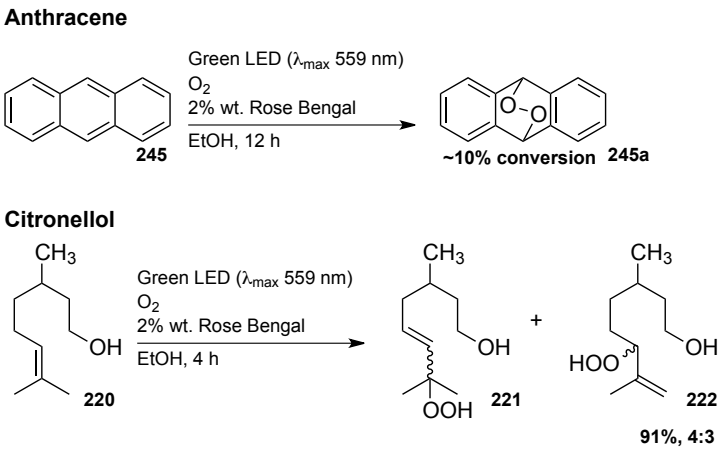
In a broader test of the applicability of the LED photo-reactors, a small series of dienes that gave a representation of [2+4] cycloadditions with $^1O_2$ were investigated. The compounds selected were α-terpinene (**223**), ergosterol (**244**) and anthracene (**245**), which are commonly all used in studies focused on oxidations with $^1O_2$. The oxidation of α-terpinene (**223**) produced endoperoxide **224** in a 99% yield after purification (Scheme 56). This oxidation took place at room temperature and was completed after 2 h consistently on scales from 100 mg to 1 g. The green LED/Rose Bengal system and the red LED/methylene blue system were both explored and both gave consistent results. On scaling the reaction up to 20 g of α-terpinene (**223**) in a 200 mL green LED reactor, the reaction was much slower and after 4 h resulted in a 1:1 mixture of the starting α-terpinene to endoperoxide **224**. This scaled-up reaction was not left to go to completion but was an example of the scale of the reaction that can be performed. Ergosterol (**244**) is a steroidal alcohol, or sterol, that contains a 1,3-diene in the B ring. On exposure to UV light ergosterol undergoes photolysis to produce vitamin D_2 as a result of electrocyclic ring opening of the B ring followed by a 1,7-hydride shift. Typically, when ergosterol (**244**) was used in $^1O_2$ studies it gave a complex mixture of products with the major compound usually being endoperoxide **246**.[111,112] With the continuing theme of the LED photoreactors not producing UV light or significant heat, it was postulated that oxidising ergosterol (**244**) in the LED reactor would only give a single compound. On reaction of 100 mg of ergosterol (**244**) in the green LED photoreactor with Rose Bengal as the sensitiser crystalline endoperoxide **246** was produced in 79% yield after purification by flash

column chromatography on silica gel (Scheme 56). This result was significant as it was a very clean transformation and represents the highest yield of endoperoxide **246** in the literature to date.



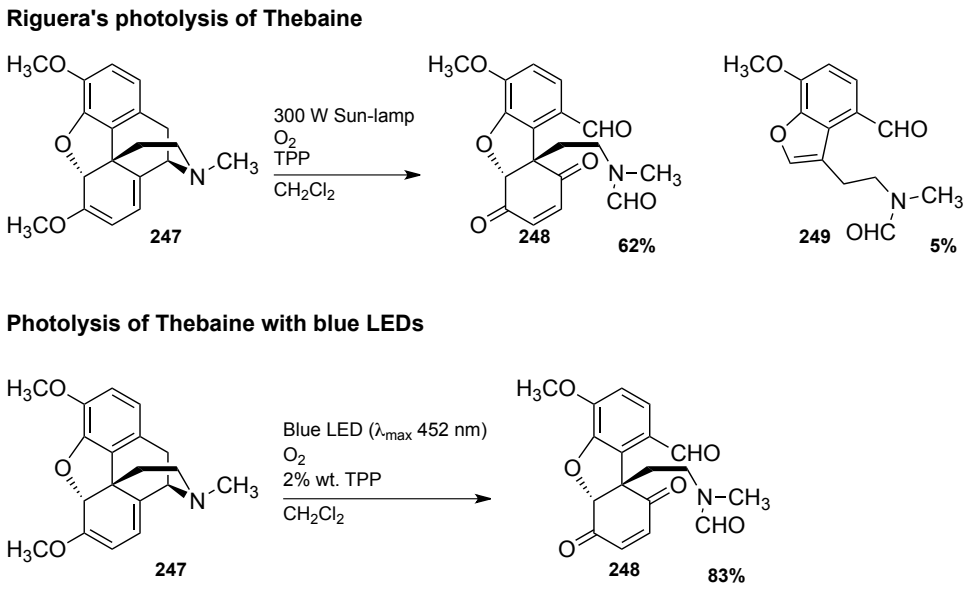
Scheme 56: *The photo-oxidations of α-terpinene (**223**) and ergosterol (**244**)*

Anthracene (**245**) was also attempted in the LED photo-reactors, however, results were unimpressive compared to the previously tested dienes (Scheme 57). While it has been commonly included in $^1O_2$ studies, it reacted extremely slowly in the present study. This is likely due to the large steric bulk around the diene. Citronellol (**220**) was also treated under the LED photo-oxidation conditions as an example of an ene-reaction (Scheme 57). This proceeded exceptionally well to give a combined yield of 91% of the secondary (**222**) and tertiary (**221**) peroxides in a 3:4 ratio respectively. This mixture of compounds is a valuable intermediate in the synthesis of the fragrance rose oxide.[113]



Scheme 57: *The photo-oxidation of citronellol (**218**) and anthracene (**245**)*

Following methodology established by Riguera and co-workers, the photolysis of the opiate alkaloid thebaine (**247**) was also investigated.[114] Within their findings, Riguera and co-workers observed that photo-oxidation with Rose Bengal (**211**) and methylene blue (**212**) provided complex mixtures of products, however TPP (**213**) gave a much cleaner conversion and resulted in two isolated compounds, formamide **248** and formamide **249** in 62% and 5% yields respectively (Scheme 58). Formamide **249** was postulated as a further photolysis or thermolysis product of formamide **248** and given the milder reaction conditions presented within the LED system it was conceivable that a single compound could be obtained in a good yield. In the LED reactor system, blue light was the most suitable monochromatic light source for TPP; therefore the photolysis of thebaine (**247**) was attempted in the blue LED reactor with dichloromethane as the solvent. Gratifyingly, on a 200 mg scale the photolysis worked well to produce formamide **248** in an 83% yield after purification by flash column chromatography on silica gel. This reaction was completed in 2 h, with no by-products observed from the ^{1}H NMR spectrum of the crude mixture. However, when the reaction was scaled up to ~1 g of thebaine the reaction was much slower, only producing a 1:1 mixture of thebaine (**247**) to formamide **248** after 3 h. This decrease in reaction rate was likely a result of a significantly higher concentration of thebaine than in the 200 mg scale reaction.



Scheme 58: *The photolysis reaction of thebaine (**247**) under the LED photo-reactor conditions*

Riguera and co-workers also report the photo-oxidation of thebaine to 14-hydroxycodeinone TFA salt **250** in a good yield. This was deemed as a valuable result to replicate and with the success of the thebaine (**247**) photolysis this reaction was attempted. Thus, thebaine (**247**) was dissolved in dichloromethane and TFA in the blue LED photo-reactor, however on workup of the reaction it was evident that the starting material had decomposed. This reaction was repeated for less time and with less acid, yet the reaction outcome was the same. Due to the differences observed between the published results and that of the LED reactor for the photolysis of thebaine (**247**), it was likely that this reaction also requires higher temperatures to promote various reaction pathways.

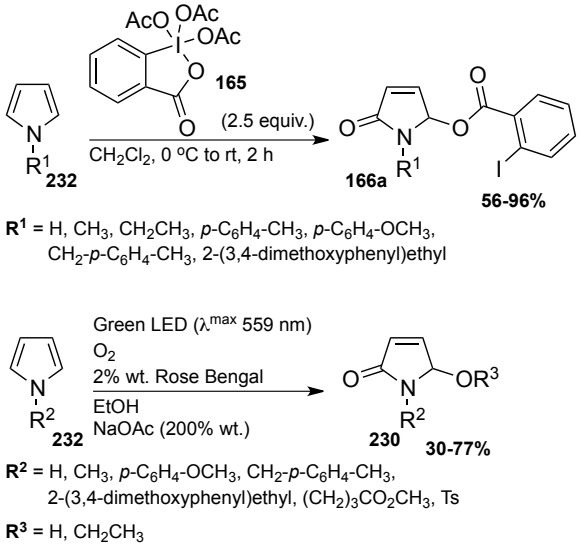
In conclusion, further validity of the broad applicability of $^1O_2$ to organic synthesis has been demonstrated with a controlled approach for the photo-oxidation of pyrrolic species. The photo-oxidation of pyrrole has been optimised to a synthetically useful yield for the first time within the literature over a broad substrate scope. This oxidation has furthermore been applied to other organic molecules, showing excellent control to $^1O_2$ oxidation products without the concern for other wavelengths interfering or heat being a significant issue.

With two significant methodologies for the controlled oxidation of pyrrole in hand, it was next desired to incorporate the oxidation of pyrrole into the synthesis of pyrrolidine alkaloids. Both methods produce a densely functionalised 2-pyrrolinone that with the appropriate chemical manipulations could undergo transformations to molecules such as preussin. This concept will be discussed in detail in the following chapter.

Chapter 4 – Applying the Oxidation of Pyrrole to Total Synthesis

4.1 Targeting preussin via the oxidation of pyrrole

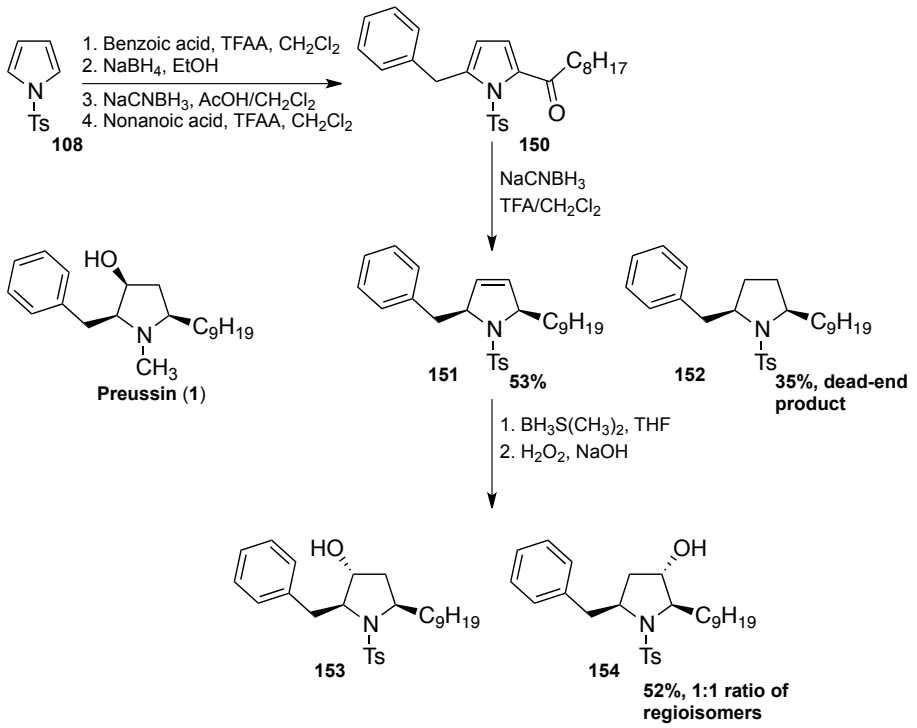
The previous two chapters comprehensively discussed the discovery of the Dess−Martin periodinane oxidation of pyrrole and the optimisation of photo-oxidation conditions that are appropriate for a range of pyrroles. These mark two significant advances in the synthetic manipulation of pyrroles by demonstrating that under appropriate reaction conditions it is possible to control the oxidation of pyrrole to 2-pyrrolinones in high to excellent yields (Scheme 59).



Scheme 59: *The reaction summary of chapter 2 and chapter 3, for the two studied pyrrole oxidation methodologies*

It was proposed that if the controlled oxidation of pyrrole to 2-pyrrolinone could be achieved, then as a test of the utility of the oxidation, the methodology should be employed in a synthesis towards a natural product. This aim followed an approach exclusively focusing on post oxidation manipulations of the 2-pyrrolinones prepared *via* the Dess−Martin periodinane methodology, rather than the 2-pyrrolinones produced from the LED photo-oxidation. This oxidative starting-point was chosen due to several reasons including that the yield was generally higher from the Dess−Martin periodinane oxidation and that a single compound was rapidly generated under these conditions without the need for post reaction manipulation, which simplified analysis. However, the photo-oxidation methodology would

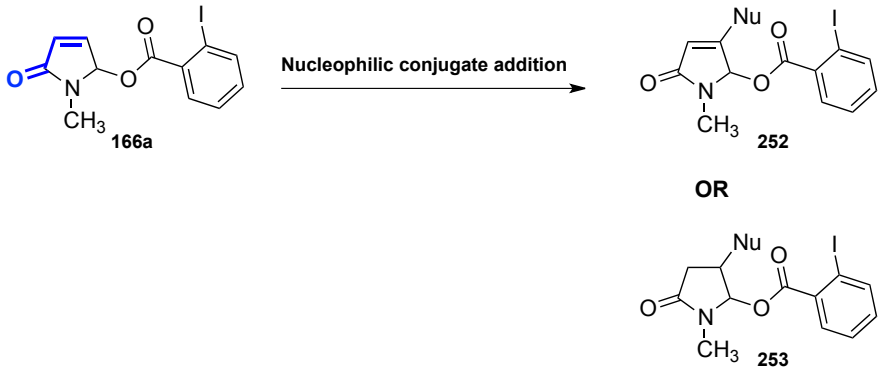
provide a good alternative for the economical generation of 2-pyrrolinone starting material once a synthetic sequence was established. To test the utility of the controlled oxidation of pyrrole, the natural product preussin (**1**) was chosen as a synthetic target. This natural product was introduced and comprehensively reviewed in chapter 1, and as discussed in chapter 2 this target was the focus of a study on the partial reduction of pyrrole, however, was not attained. The reason behind this was due to limitations and synthetic restrictions of the methodology. This included over-reduction of the pyrrole **150** to pyrrolidine **152**, which was a dead-end product in the synthetic sequence towards preussin, and the lack of alkene selectivity in 3-pyrroline **151**, resulting in a equal mixture of functionalised pyrrolidines (Scheme 60). It was hypothesised, then, that if the oxidation of pyrrole could be achieved feasibly, then preussin could possibly be obtained from a different synthetic sequence involving an oxidation of pyrrole as the key synthetic step.



Scheme 60: *The attempt to preussin from reduction chemistry*

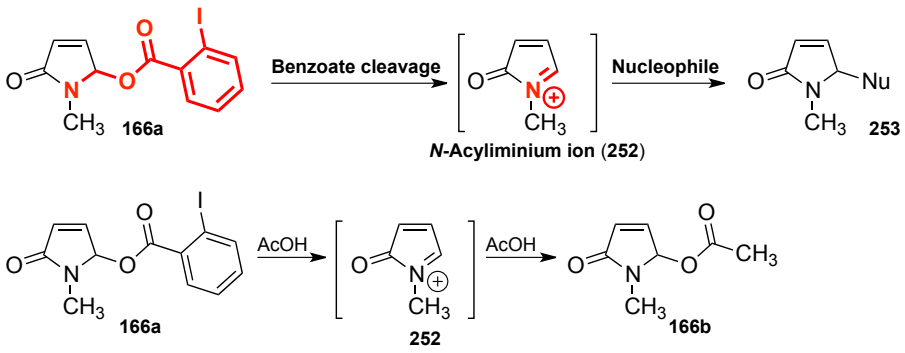
Examination of the structure of the resulting 5-aroyloxy-2-pyrrolinones from the Dess−Martin periodinane controlled oxidation of pyrrole saw a more diverse suite of synthetic handles than were present in 3-pyrrolines. Firstly, the oxidations were amenable towards electron-rich pyrrolic systems with alkyl or aryl substitution at the nitrogen. This offered value to the synthesis of preussin, which contains an *N*-methyl

group. In examining the synthetic handles within the 5-aroyloxy-2-pyrrolinones it was observed that selective functionalisation post oxidation could be possible; for example the α, β-unsaturated amide was a versatile moiety that could be harnessed for conjugate additions, such as the Michael addition or a regioselective mono-hydroxylation (Scheme 61).



Scheme 61: *An illustrative example of how the amide could be taken advantage of*

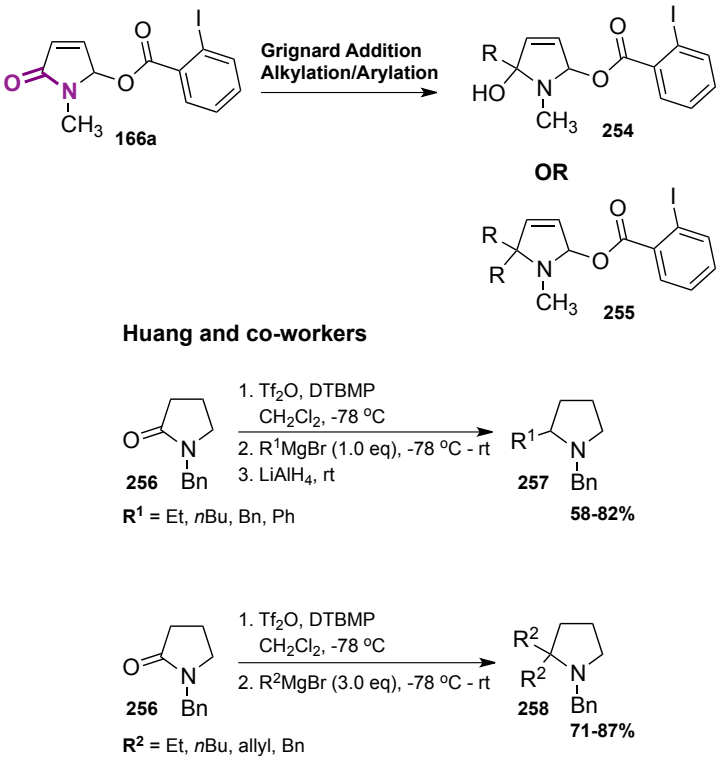
The aroyloxy functionality at the C5 position of the ring provided a unique synthetic handle. For example, upon cleavage of the aroyloxy group, the generation of the *N*-acyliminium ion **252** could occur, which in turn could be captured by an appropriate nucleophile to selectively install functionality at the C5 position of the ring (Scheme 62).[115,116] This methodology has been observed on these compounds previously with the production of 5-acetoxy-2-pyrrolinone **166b** from 5-aroyloxy-2-pyrrolinone **166a** on treatment with acetic acid (Scheme 62).



Scheme 62: *Illustrative example of N-acyliminium ion chemistry*

The final functional group of note was the amide itself. This convenient synthetic handle could be used for alkylation or arylation *via* a Grignard addition or could be reduced selectively to give a hemiaminal or amine (Scheme 63). Methodology for

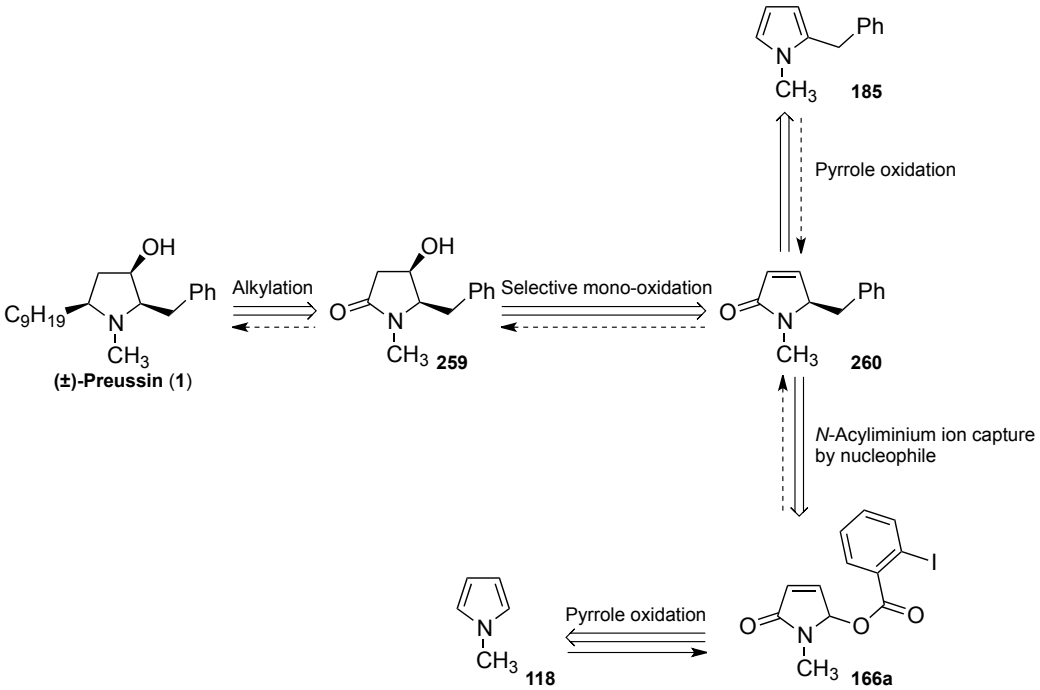
the addition of an organometallic reagent to the amide of a 2-pyrrolinone or 2-pyrrolidinone was not common within the literature, as typically methodology of this type tends to add into the amide of a maleimide or succinimide. However, Huang and co-workers have recently reported methodology that forms a new C−C bond at the amide carbonyl of 2-pyrrolidinones on treatment with various Grignard reagents.[117,118] They report that on addition of one equivalent of a Grignard reagent followed by *in situ* reduction of the hemiaminal then mono-alkylation or arylation was achieved, while on addition of a molar excess of a Grignard reagent di-alkylation was observed (Scheme 63).



***Scheme 63**: Illustrative example of alkylation or arylation from a Grignard reagent. Huang and co-workers methodology*

With the synthetic handles introduced above in mind, a retrosynthetic analysis of preussin (**1**) was performed. The analysis deliberately focused on making disconnections towards a 2-pyrrolinone starting material. Scheme 64 illustrates the disconnections that were made starting from the disconnection of the nonyl side-chain at the C2 carbon. It was postulated that this functionality could be installed using a Grignard reagent, following the methodology developed by Huang and co-workers.[118] A disconnection of the hydroxyl group could be possible, leading back to

the 5-benzyl-2-pyrrolinone **260**; while the installation of the hydroxyl functionality could be a result of a regioselective hydroboration assisted by the electronics of the α, β-unsaturated amide. Examination of 5-benzyl-2-pyrrolinone **260** revealed that it could be assembled *via* two different routes. The first route considered was direct oxidation of 2-benzyl-*N*-methylpyrrole **185**, which after post oxidation manipulation could produce 5-benzyl-2-pyrrolinone **260**. The second synthetic sequence could see a further disconnection at the C5 position of the ring, which would result in starting from *N*-methyl-2-pyrrolinone (**166a**), the oxidation product of *N*-methylpyrrole (**118**). Focusing on the forward direction from *N*-methyl-2-pyrrolinone (**166a**), it was conceivable that cleavage of the aroyloxy group would produce an *N*-acyliminium ion, which could in turn be captured by an appropriate benzyl nucleophile.



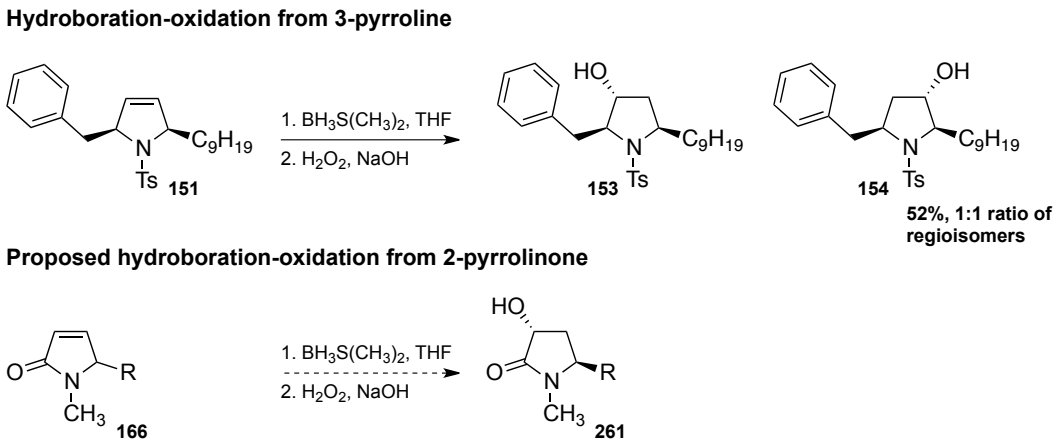
Scheme 64: *Retrosynthetic analysis making disconnections from preussin (**1**) towards a 2-pyrrolinone starting material*

The stereochemical outcome of the synthesis of preussin was important, however during the course of the project it was decided to only concentrate on the relative stereochemistry around the ring, rather than develop an asymmetric synthesis. Furthermore, it should be noted that while the stereochemical outcome of each step was extremely important, the overall construction of the molecular scaffold was the most important to initially focus on. Thus, the following discussion focuses on the

introductory accounts of the attempts at using the 2-pyrrolinone systems in the total synthesis of preussin and other pyrrolidine like alkaloids.

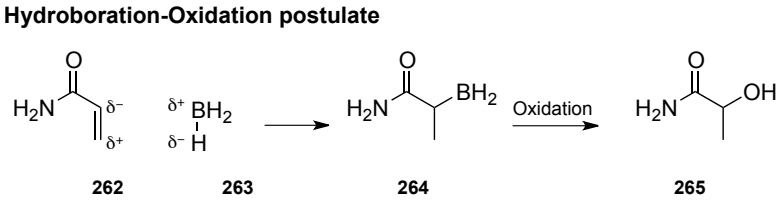
4.2 Oxidation at the C3 and C4 position

One of the significant weaknesses of using the partial reduction of pyrrole methodology in the targeted synthesis of preussin was the lack of bias between the alkene carbons at C3 and C4. This lack of bias between the two alkene carbons was only apparent when considering the 2,5-disubstituted-3-pyrroline **151**, and when the hydroboration-oxidation methodology was applied to the molecule, a 1:1 mixture of regioisomers was produced. It was proposed that using a 2-pyrrolinone as the starting point then selective hydroboration-oxidation could be achieved to install hydroxyl functionality at C3 (Scheme 65).



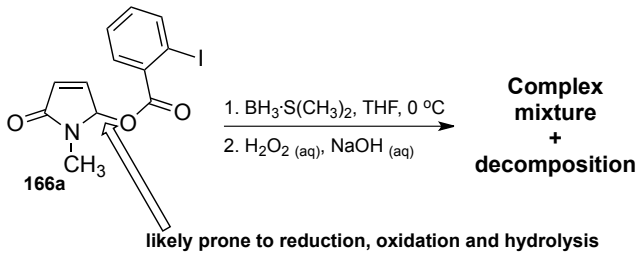
Scheme 65**: Proposed hydroboration-oxidation methodology on 2-pyrrolinone **166a

Due to the polarity across the α, β-unsaturated amide present in the 2-pyrrolinone, selective addition to the alkene could take place. Conceptually, during the concerted reaction, the partial negative charge of the α-carbon (i.e. C3) should attract the partial positive charge of the boron, giving selectivity towards the C3 oxidation over the C4 oxidation. However, there was a distinct lack of information in the literature for hydroboration reactions on α, β-unsaturated amides, which was likely due to boranes acting as amide reducing agents.[119]



Scheme 66:*The proposed hydroboration-oxidation reaction to be applied to the 2-pyrrolionone*

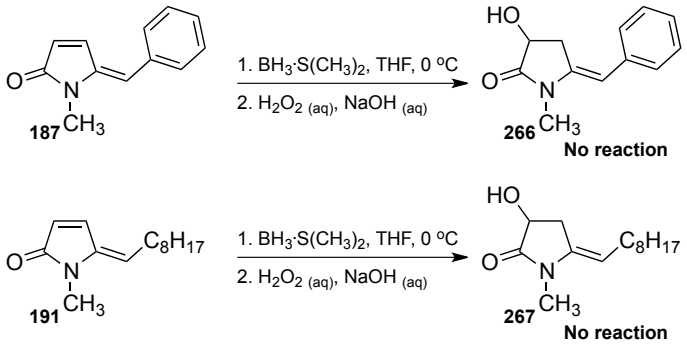
Following the method established by Brown, hydroboration-oxidation was initially attempted on *N*-methyl-2-pyrrolinone **166a**.[120] There were concerns that this starting material was a poor candidate for the mono-hydroxylation methodology due to the arlyoxy functionality at C5 having the propensity to undergo reduction from the borane, oxidation from the peroxide or undergo base assisted hydrolysis. It was not surprising then, that on treatment with a 2 M solution of borane-dimethyl sulfide complex at 0 °C in THF, followed by treatment with aqueous sodium hydroxide and hydrogen peroxide, that only a complex crude reaction mixture could be recovered in a poor yield (Scheme 67). It was hypothesised that the low mass of the recovered material was likely due to hydrolysis and reduction products being formed.



Scheme 67: *The attempted hydroboration-oxidation of 2-pyrrolinone* ***166a***

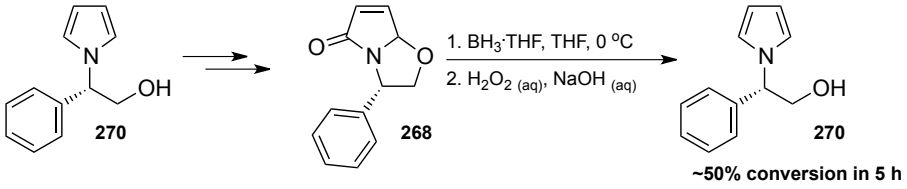
It was suggested that a better candidate for attempting the hydroboration-oxidation methodology would be a system without a sensitive functional group at C5. Thus, the 5-substituted-2-pyrrolinone **187** was subjected to the reaction conditions (Scheme 68). However, after workup of the reaction mixture, analysis of the ^{1}H NMR spectrum suggested that no reaction had taken place. The reaction was repeated over a longer reaction time and with the 5-substituted-2-pyrrolinone **191**, yet in both instances there was no evidence to suggest that reaction had taken place (Scheme 68). While it was good to be able to recover starting material, it was clear that the 5-substituted-2-pyrrolinones species were unreactive under these reaction conditions,

which was likely a result of the conjugation within the starting material - although it was surprising that no reaction occurred on the alkylidene alkene.



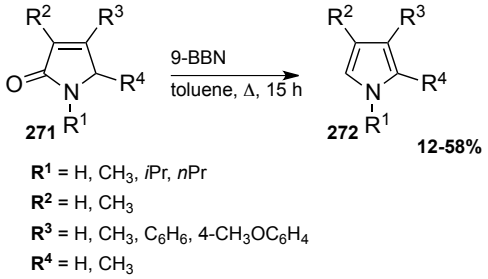
Scheme 68: *The failed attempts at hydroboration-oxidation of 5-substituted-2-pyrrolinones* ***187*** *and* ***191***

As a last effort, bicyclic 2-pyrrolinone **268** was exposed to the reduction conditions. This compound was synthesised in a parallel study from the cyclisation of the oxidation product of the pyrrole synthesised from (S)-phenylglycinol (**269**). While there was an ether linkage present at C5 that could be prone to chemical manipulation, the material appeared to be a nice compromise between the previous two attempts. This was justified as the bicyclic 2-pyrrolinone **268** did not possess the conjugation of the 5-alkylidene-2-pyrrolinones, and if any hydrolysis or reduction products were obtained, they should be present in the molecule due to the tether through nitrogen. Thus, bicyclic 2-pyrrolinone **268** was treated under slightly modified conditions, substituting the borane-dimethyl sulfide complex with 1 M borane-THF complex. On analysis of the ^{1}H NMR spectrum of the crude reaction mixture a significant amount of starting material was observed, however pyrrole **270** was identified as the major product (Scheme 69). This product was likely a result of reduction of the 2-pyrrolinone to the pyrrole by the borane. This result was interesting, providing information as to why the reactions were not behaving previously; but disappointingly it also provided justification to not continue investigating the hydroboration-oxidation methodology on 2-pyrrolinones.



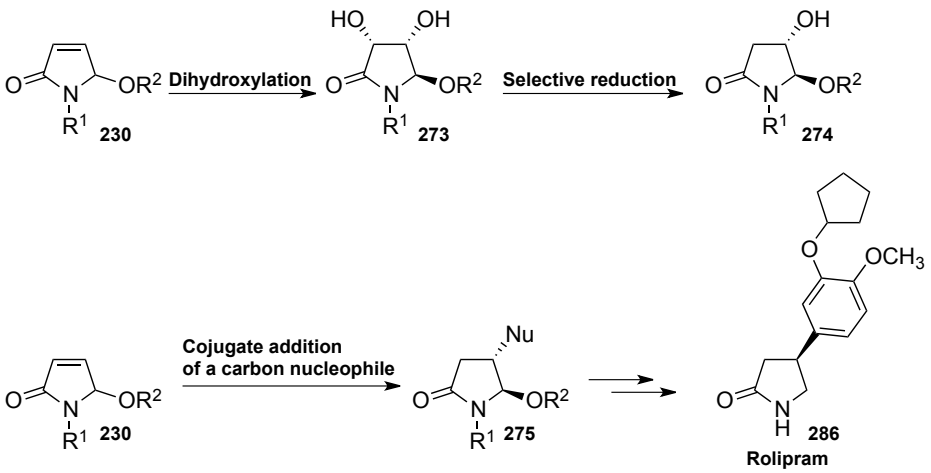
Scheme 69: *The reduction of bicyclic 2-pyrrolinone* ***268*** *under hydroboration-oxidation conditions*

Reductive methodology similar to what was observed has been identified within the literature, albeit not commonly, by De Kimpe and co-workers.[121,122] In their research they demonstrate that 3-substituted-2-pyrrolinones **271** (a product from the condensation of an amide and a ketone) produce 3-substituted pyrroles **272** in low to moderate yields on treatment with 9-BBN in toluene at reflux overnight.



Scheme 70: *DeKimp and co-workers reduction of 2-pyrrolinone* ***271*** *to pyrrole* ***272***

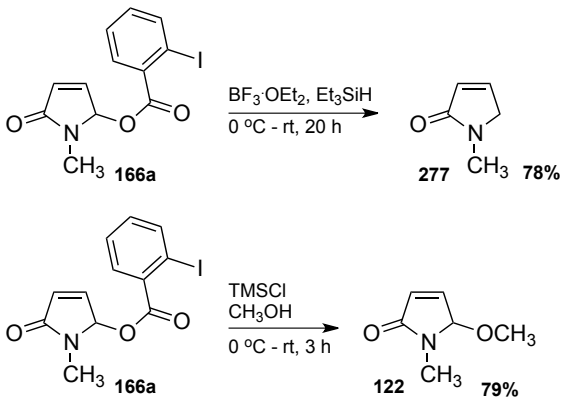
The reduction of 2-pyrrolinone to pyrrole was ultimately a disappointing result as it provided a dead-end pathway in the synthetic scheme. While the mono-hydroxylation was abandoned at this stage, it is not to say that other selective conjugate additions are not be possible on the 2-pyrrolinone systems. As a potential solution to the lack of selective mono-oxidation at C3, it was postulated that a direct oxidation event could take place across the alkene **230** to produce the C3/C4 dihydroxyl species **273**, before a selective reduction at C3 or C4 (Scheme 71). Furthermore, there was still opportunity for the selective nucleophilic addition across the α, β-unsaturated amide with the conjugate addition of carbon or sulfur nucleophiles, which would rapidly generate structures analogous to rolipram (**276**), a selective phosphordiesterase-4 inhibitor.[123] While these potential routes were interesting to explore, they would likely not lead to an efficient synthesis of preussin and were not investigated during the present study.



Scheme 71: *Examples of other methodology to be explored in future studies*

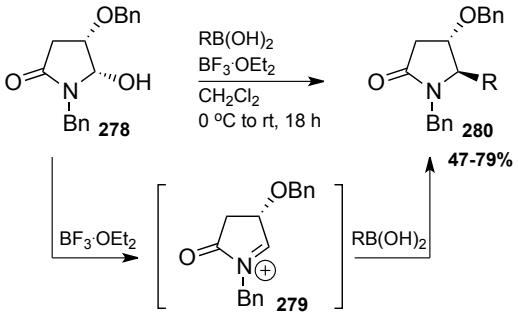
4.3 N-Acyliminium ion methodology

One advantage to oxidising pyrrole compared to partially reducing pyrrole was the installation of a convenient synthetic handle at the C5 position in the form of an ether or acetoxy group. This handle was significant as on cleavage of the labile functional group, generation of the electrophilic *N*-acyliminium ion was possible. This ion can be generated *in situ* and can be captured by a nucleophile to produce a molecule with a newly formed Nu−C bond at the C5 position. As already seen, this concept was applied to generate the 5-acetoxy-2-pyrrolinone **166b** on treatment of 5-aroyloxy-2-pyrrolinone **166a** with acetic acid (Scheme 72). Further to this, reactions taking advantage of this concept had taken place with the reduction at C5 by adding a Lewis acid to generate the *N*-acyliminium ion before capturing with a hydride to produce 2-pyrrolinone **277** and also treating 2-pyrrolinone **166a** with methanolic HCl to generate the 5-methoxy-2-pyrrolinone **122** (Scheme 72).



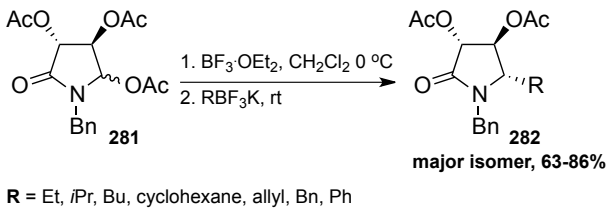
Scheme 72: *Taking advantage of the N-acyliminium ion*

The concept of generating an *N*-acyliminium ion followed by nucleophilic capture can be expanded further to carbon nucleophiles and this concept has been utilised extensively throughout the literature and was thoroughly discussed in a review by Yazici and Pyne in 2009.[115,116] After a search through the literature it was apparent that there were numerous methods that could be appropriate to targeting preussin (**1**). Methodology of immediate note was the research reported by Pyne and co-workers who utilise the Petasis borono-Mannich reaction to couple a variety of boronic acids to 2-pyrrolinone **282** (Scheme 73).[124]



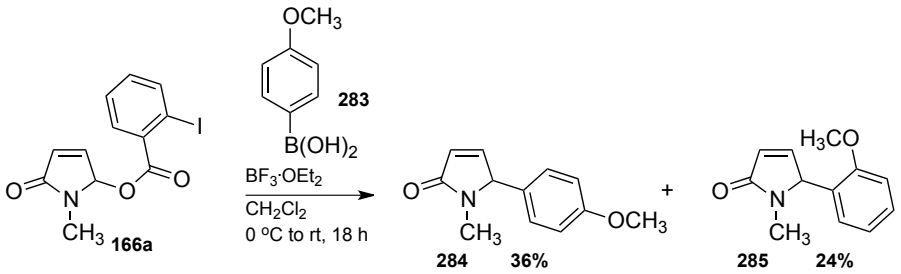
Scheme 73: *Petasis borono-Mannich methodology developed by Pyne and co-workers*

The reaction described by Pyne and co-workers went through an *N*-acyliminium ion intermediate (**279**), which was subsequently captured by boronic acid nucleophiles. Treating 2-pyrrolidinone **278** with BF_3•OEt_2 generated the *N*-acyliminium ion with the boronic acid being delivered on the opposite face to the functionality at C4, allowing for stereochemical control. Stefani and co-workers have adopted similar methodology using potassium organotrifluoroborates in the place of boronic acids to produce a wide range of molecules containing newly installed aryl and alkyl functionalities (Scheme 74).[125,126] Both of these methods were amenable to the synthesis of preussin (**1**), which required a nonyl or a benzyl group at C5.



Scheme 74: *Stefani and co-workers capturing of an N-acyliminium ion with organotrifluoroborates*

The Petasis borono-Mannich methodology developed by Pyne and co-workers was attempted on 2-pyrrolinone **166a**. In dry dichloromethane, a mixture of 2-pyrrolinone **166a** and *p*-methoxyphenylboronic acid (**283**) was treated with $BF_3{\cdot}OEt_2$ at 0 °C. The reaction mixture was left to stir overnight and on workup, analysis of the ^1H NMR spectrum of the crude reaction mixture showed reasonably clean conversion to two products. On purification and analysis it was evident that these two products were 5-(*p*-methoxyphenyl)-2-pyrrolinone **284** and 5-(*o*-methoxylphenyl)-2-pyrrolinone **285** in a 36% yield and a 24% yield respectively (Scheme 75).



Scheme 75: *The attempted Petasis borono-Mannich reaction on 2-pyrrolinone* ***166a***

The two regioisomeric products were an unexpected result as it was anticipated that the boronic acid would direct the regioselectivity of the reaction, however, that did not appear to be the case. It was evident that the *N*-acyliminium ion had been generated on reaction with the Lewis acid, however instead of reacting with the boronic acid it appeared that the arene was capturing the *N*-acyliminium ion without consideration for the boronic acid functionality.

The two compounds were primarily identified by analysis of the ^1H NMR spectrum. The compound assigned as 5-(*p*-methoxyphenyl)-2-pyrrolinone **284** was observed to contain a *p*-methoxyphenyl group by the two doublets integrating for two protons each at 6.89 ppm and 7.04 ppm that were assigned to the aromatic protons, and the singlet resonance at 4.92 ppm, which likely represented the methoxy-protons.[82] Concerning the 2-pyrrolinone ring, the three protons were all shifted upfield compared to the starting material with the resonance for the proton at C5 showing the biggest shift down to 4.92 ppm. While this was a large shift, it was typical for a proton in this environment.[82] The compound assigned as 5-(*o*-methoxyphenyl)-2-pyrrolinone **285** was observed to contain an *o*-methoxyphenyl group, with the diagnostic multiplet at 6.85-6.96 ppm integrating for three protons and a doublet of

triplets at 7.30 ppm integrating for one proton, with the singlet at 3.89 ppm being assigned as the methoxy protons. Again a large upfield shift was observed for the proton at C5, however it was not of the magnitude that was observed in 5-(*p*-methoxyphenyl)-2-pyrrolinone **284**, which was likely a result of the methoxy group shielding the proton in 5-(*o*-methoxyphenyl)-2-pyrrolinone **285** (Figure 22). Furthermore, on analysis of the ^{13}C NMR spectrum of each of the compounds, the 5-(*p*-methoxyphenyl)-2-pyrrolinone **284** had a total of ten carbon resonances with four observed CH signals due to the symmetry of the methoxyphenyl group, where as 5-(*o*-methoxyphenyl)-2-pyrrolinone **285** was observed to have twelve carbon resonances with six CH signals.

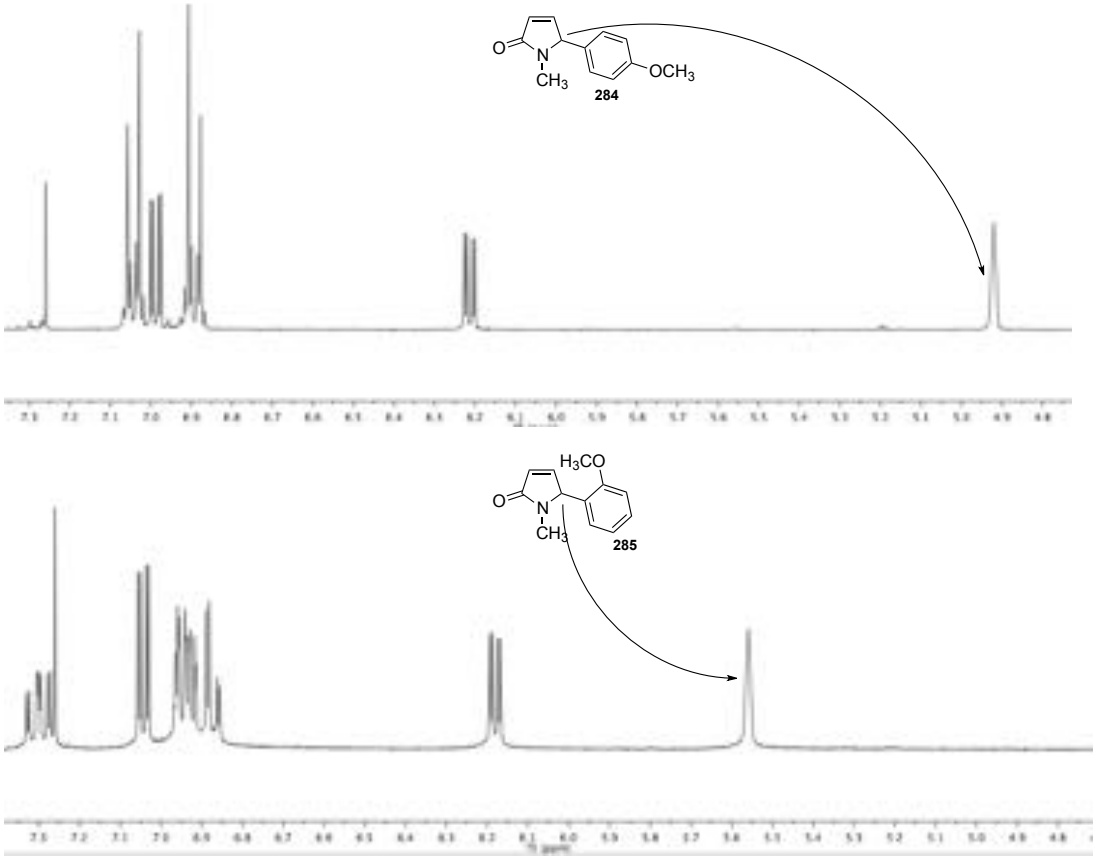
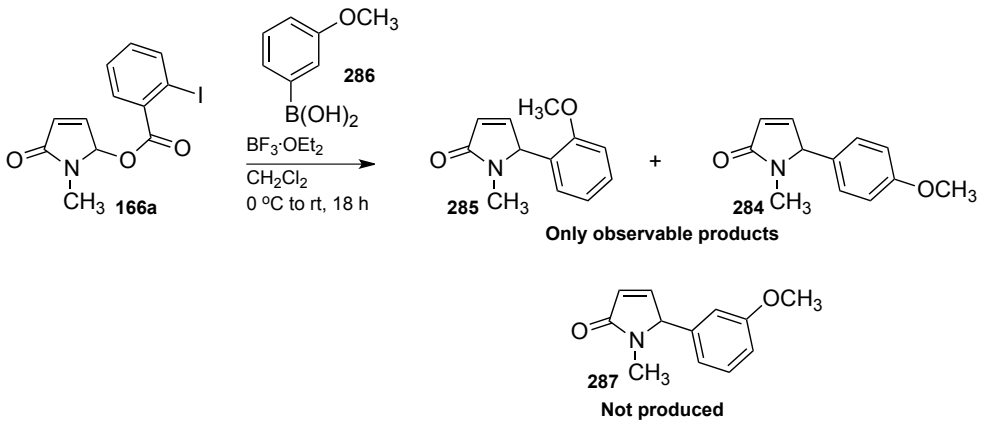


Figure 22: *Comparison of the two ^{1}H NMRs of 5-(p-methoxyphenyl)-2-pyrrolinone **284** and 5-(o-methoxyphenyl)-2-pyrrolinone **285** to illustrate the shielding effect on the C5 proton.*

The first consideration into why the reaction behaved differently to the literature was the quality and purity of the boronic acid used, however, after analysis of the starting material by ^{1}H NMR it was deemed pure. The next consideration was that potentially under the strong acidic conditions, deboronation had occurred to give

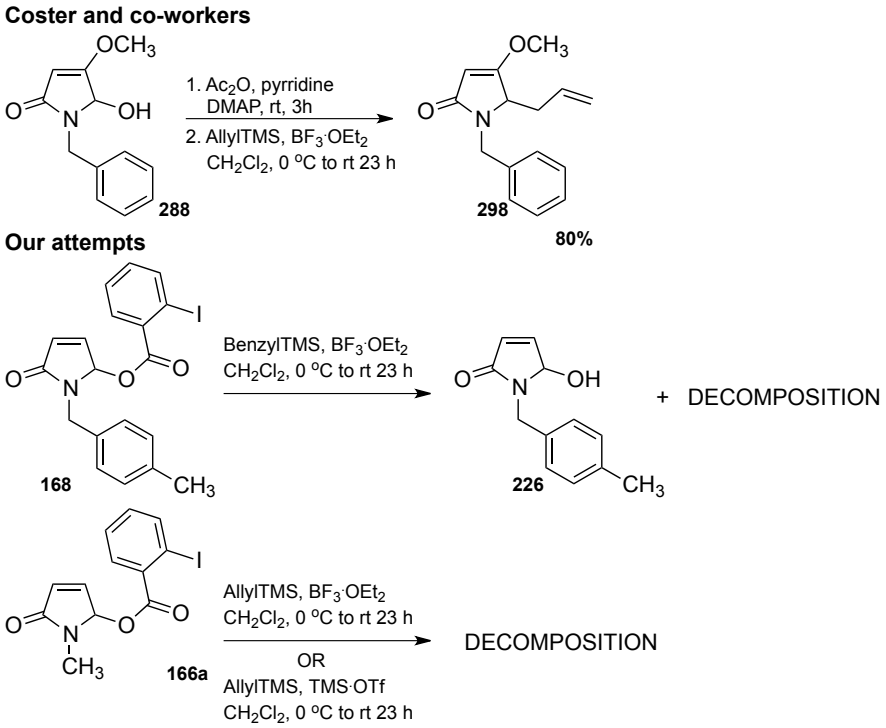
methoxybenzene, which reacted as the nucleophile. This was a well-known phenomenon, however, it was only commonly reported to occur in the presence of Brønsted acids and not with Lewis acid due to the requirement of an acidic proton source.[127] This also seemed unlikely, as it has never been reported as a consideration in the publications detailing reaction with a *N*-acyliminium ion with boron based nucleophiles. However, as a test to see whether it was the high concentration of Lewis acid changing the reaction outcome, the reaction was repeated at a higher dilution, yet this resulted in the same product distribution as observed previously. Order of addition was also tested, with 2-pyrrolinone **166a** being treated with $BF_3{\cdot}OEt_2$ for 30 min before addition of boronic acid **283**, however, the same outcome was observed. As a final test, *m*-methoxyphenylboronic acid **286** was used in the reaction to assess whether any Petasis borono-Mannich product was being generated. Again, only the *ortho*- and *para*-products were observed, providing evidence to suggest that the reaction was going through a different reaction mechanism entirely (Scheme 76).



Scheme 76: *An experiment with m-methoxyphenylboronic acid, producing only the o- and p-methoxy-2-pyrrolinones **284** and **285***

A consideration was hypothesised that the difference in reactivity could be attributed to the difference in starting material between the attempted reaction and those present within the literature. It was conceivable that the alkene moiety across C3−C4 was generating a more reactive electrophilic *N*-acyliminum ion that rapidly reacted with the arene instead of the boronic acid. Within the literature there were only a few examples of using a 2-pyrrolinone in these types of reactions instead of using a 2-pyrrolidinone. One of note was the work by Coster and co-workers, who had

electron-donating substitution at the C4 position of the 2-pyrrolinone (Scheme 77).[92] They successfully report coupling with allyl-TMS as the nucleophile in an 80% yield. Thus, it was hypothesised that perhaps a TMS-nucleophile would act more appropriately with an *N*-acyliminium ion of this structure.

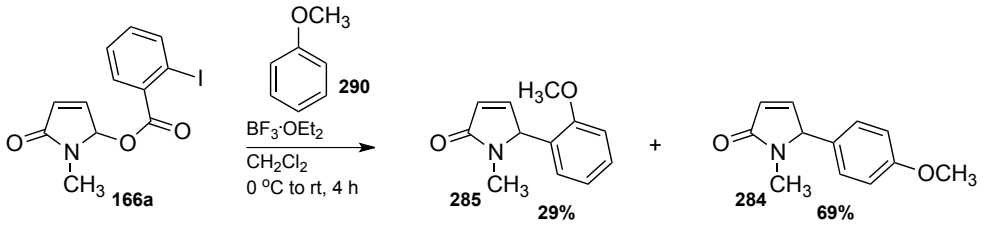


Scheme** 77: Costa and co-workers capture of an N-acyliminium ion with a TMS nucleophile and the results of following the methodology with **166a** and **168

As Coster and co-workers only reported successful coupling with allyl-TMS and the *N*-benzyl substituted 2-pyrrolinone **288**, the experiment was attempted on *N*-(4-methylbenzyl)-2-pyrrolinone **168**. As preussin (**1**) has a C5 benzyl group, it was decided to use the benzyl-TMS instead of the allyl-TMS used by Coster, yet the methodology was followed precisely apart from this modification. Unfortunately, the reaction consisted mostly of decomposition and a small isolable amount of the hydroxyl species **226**, which was likely a result of hydrolysis of the aroyloxy or water acting as a nucleophile on workup. The methodology was also attempted on the *N*-methyl-2-pyrrolinone **166a**, with allyl-TMS, and with a different Lewis acid, however, only decomposition was observed in these cases.

The above collection of trial reactions, while disappointing, did lead to an interesting discovery in the way that boronic acids seemed to behave following a Friedel−Crafts

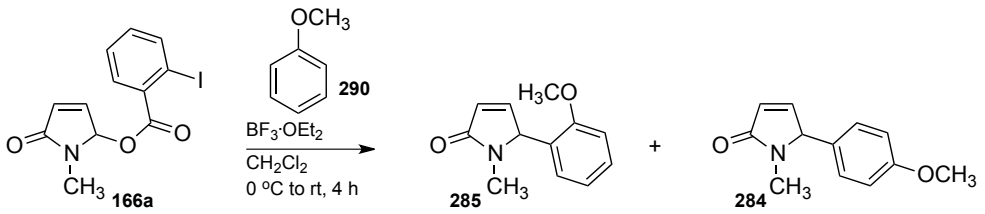
acylation type mechanism rather then the Petasis borono-Mannich mechanism that was required for selectivity. To probe this idea further, the reaction was performed with methoxybenzene (**290**), as the nucleophile. On workup of this reaction, it was evident that the reaction had worked well in a Friedel−Crafts acylation, giving the *ortho*-product **285** and the *para*-product **284** in an approximately 1:4 ratio in a 98% isolated yield (Scheme 78).



Scheme 78: *The Friedel−Crafts acylation of methoxybenzene with a N-acyliminiun ion*

This was an excellent result and it supported the earlier results of the attempted Petasis borono-Mannich reaction, which possibly reacts through a Friedel−Crafts acylation reaction followed by deboronation as there was no identification of the normal Petasis borono-Mannich reaction product. In an attempt to get further selectivity towards to *para*-methoxylphenyl products **284**, which would serve as a potential precursor to other alkaloids such as codonopsinine (**3**), a screen of readily available Lewis acids was conducted (Table 5).

Table 5: *Lewis acid screen in an attempt to promote para-selectivity*



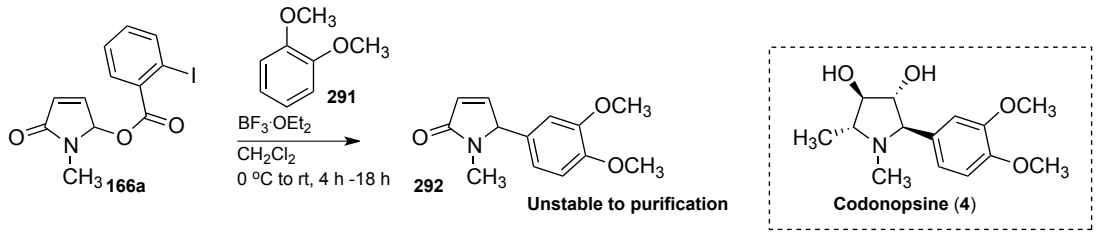
Lewis acid	**Result**	**Ratio of 285 to 284[a]**
BF_3•OEt_2	Quantitative yield	1:4
$Bi(NO_3)_3$	Starting material + decomposition	-
$ZrCl_4$	Starting material + decomposition	-
$ZnCl_2$	Starting material + decomposition	-
$AlCl_3$	<10 % product	1:3
$TiCl_4$	Starting material + decomposition	-
$Sc(OTf)_2$	Decomposition	-
$CoCl_2$	Starting material	-
TMSOTf	~65 %	5:2
$InBr_3$	~50 %	2:3
$Bi(OTf)_3$	~35 %	1:1
$Cu(OTf)_2$	Starting material	-

a.) Ratio was determined by analysis of the ^{1}H NMR of the crude mixture.

While the screen provided some interesting cases, it was evident that the use of BF_3•OEt_2 was the most successful, in both the yield of the reaction and the *para*-isomer selectivity. Of significant note, was the result observed from using TMSOTf as the Lewis acid. In this experiment the amount of the *ortho*-product **285** was significantly larger than that of the *para*-product **284**, which was the opposite of what was predicted or observed in most other cases. This was also partially

expressed in the use of $Bi(OTf)_3$ as the Lewis acid, which resulted in an approximate 1:1 ratio of the two products. However, as each Lewis acid that generated product gave a vastly different ratio of products it was difficult to imply any mechanistic meaning from these results.

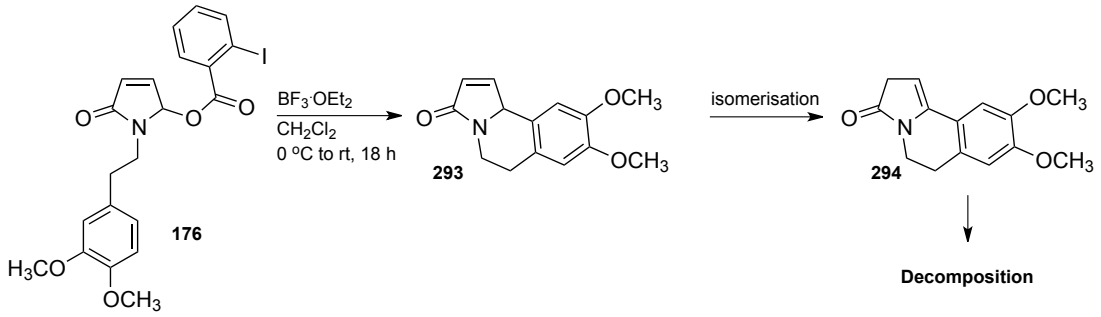
With the desire to utilise the Friedel−Crafts acylation in a targeted synthesis, 1,2-dimethoxybenzene (**291**) was substituted in the reaction as the nucleophile as it would give a single product due to the directing groups around the ring and it would install the correct functionality in the C5-position for the alkaloid codonopsine.



Scheme 79: *The synthesis of the C5-substituted 2-pyrrolinone **292** as an intermediate in the attempted synthesis of codonopsine (**4**)*[5-7]

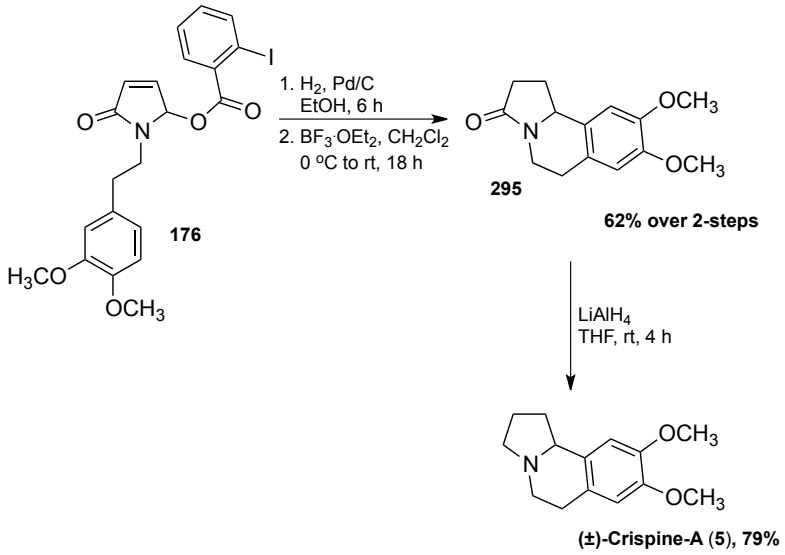
Again this reaction proceeded well with the production of a single isomer of the C5 substituted 2-pyrrolinone **292**, in a quantitative conversion. However, as a minor frustration the compound was unstable to purification on silica gel and on standing. As it was deemed that the compound would not survive long enough for reactions past the acylation step, a different target was approached. It was hypothesised that the natural product crispine A (**5**) could be targeted from the intramolecular acylation of 2-pyrrolinone **176**, which was generated in a 96% yield from the parent pyrrole **175**. Thus, 2-pyrrolinone **176** was treated with $BF_3{\cdot}OEt_2$ in dry dichloromethane to produce the tricyclic core of crispine A (Scheme 80). On analysis of the ^{1}H NMR spectrum of the crude reaction mixture, there appeared to be two major compounds, **293** and **294**. On purification only the isomerised **294** was isolated, which was identified by the diagnostic resonances in the ^{1}H NMR spectrum with a triplet integrating for one proton at 5.45 ppm and a doublet integrating for two protons at 3.24 ppm. These two resonances coupled to each other and were assigned as the C4 and C3 protons around the pyrrolinone ring. This isomerisation and diagnostic resonances were supported by a similar observation by Dïach and co-workers.[128] The system reported by Dïach and co-workers only differed by not having functionality

on the benzene ring, and while they did not observe any evidence for decomposition in the present study rapid decomposition was observed, again limiting the utility of the product.



Scheme 80: *The attempted acylation towards crispine A with the observed isomerisation and decomposition*

As crispine A (**5**) does not have functionality across the C3−C4 carbons, it was suggested that removing the double bond *via* catalytic hydrogenation before the cyclisation would prevent any isomerisation leading to decomposition while still producing a useful intermediate towards the target. Thus, a catalytic hydrogenation was performed on 2-pyrrolinone **176** before the acylation reaction, to produce 2-pyrrolidinone **295** in a 62% yield over two steps (Scheme 81). This 2-pyrrolidinone was well documented in the literature and only required an amide reduction to yield the natural product.[129,130] This reduction was performed with $LiAlH_4$ to produce racemic crispine A in a 79% yield, or a 47% yield over four steps from the parent pyrrole.

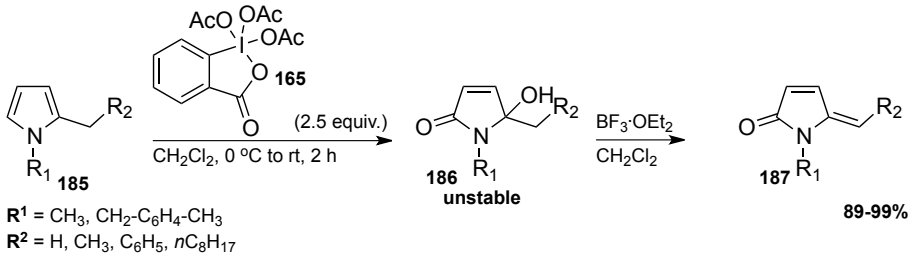


Scheme 81: *The synthesis of racemic crispine A (**5**) from pyrrole*

While it was again disappointing that the regioselective *N*-acyliminium ion reactions did not proceed as planned, some interesting methodology was explored in the Friedel−Craft acylation reaction, leading to a synthesis of a natural product. It was likely that the aforementioned regioselective methodologies did not behave in the expected manner due to the more electrophilic *N*-acyliminium ion being generated as a result of the alkene across C3−C4. To remedy this issue, it is likely that the alkene will have to be modified and removed prior to any further attempts to capture the *N*-acyliminium ion with an activated nucleophile, as was demonstrated in the synthesis of crispine A.

4.4 Reduction of 5-subsituted 2-pyrrolinones

As discussed in chapter 2, a significant issue concerning the Dess−Martin periodinane oxidation of the 2-subsitituted pyrroles was the generation of the unstable 5-hydroxy-2-pyrrolinone **186**. This species can be treated with $BF_3{\cdot}OEt_2$ to generate the highly conjugated alkylidene **187**, which was produced in a high yield over two steps (Scheme 82). While it was significant that compounds of this type can be readily produced and in excellent yields, they have been shown to be difficult to functionalise post oxidation.



Scheme 82: *Production of 5-alkylidene-2-pyrrolinones from pyrrole*

As discussed within this chapter, 2-pyrrolinones featuring alkylidene functionality at the C5-position tend to be unreactive, which was likely due to the favourable conjugation within the molecules. This lack of reactivity became a significant frustration due to the parent 1,2-dialklyated pyrroles being readily synthesised, the yield of the oxidation/elimination being higher in these compounds compared to the simple *N*-substituted pyrroles, and having access to 2-pyrrolidinones with the C5 functionality already in place would save on cumbersome reaction steps. With two distinct alkene environments present in molecules of this type it was suggested that a selective reduction could be viable, allowing for the resulting molecules to be more reactive towards further synthetic manipulation, due to the manipulation of the conjugated system. In thinking about the alkene environments present in the molecule, there was an alkene between C3−C4 that was part of an α, β-unsaturated amide that would be useful for further synthesis if selective access was available, and there was the exocyclic alkylidene that would not serve as a synthetic handle in targeting such natural products as preussin (**1**) (Figure 23).

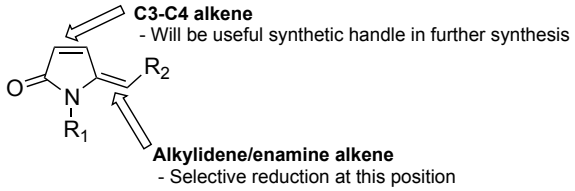
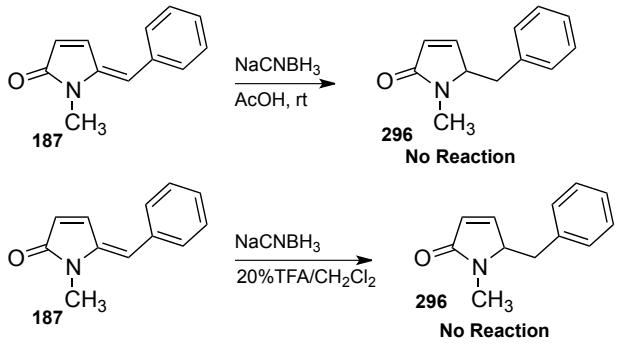


Figure 23: *Graphically depicting the two alkenes that contribute to the conjugation and potential lack of reactivity*

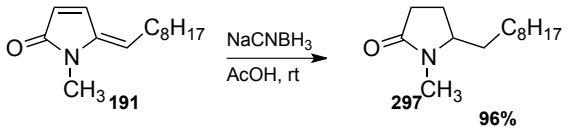
While the positioning of the alkylidene alkene meant that it was an enamide, it was proposed that it could behave as an enamine. As an enamine it would be protonated to an *N*-acyliminium ion under acidic conditions, which can be selectively reduced on treatment with sodium cyanoborohydride.[131,132] Thus, 2-pyrrolinone **187** was

dissolved in acetic acid and treated with sodium cyanoborohydride (Scheme 83). Examination of the ^{1}H NMR spectrum of the crude reaction material suggested that no reaction had taken place. Again this result was likely due to the conjugation of the alkene to the phenyl group, as protonation would require the system to be less conjugated, which was disfavoured. In an attempt to promote *N*-acyliminium formation, TFA was used as a 20% solution in dichloromethane, however this produced the same negative result.



Scheme 83: *Attempted selective reductions of alkylidene **187** on treatment with sodium cyanoborohydride under acidic conditions*

It was hypothesised that the lack of reactivity of 2-pyrrolinone **187** was likely due to the alkylidene group not only being in conjugation with the α, β-unsaturated amide but also in further conjugation with the aromatic functionality. As a result of this, the acetic acid/sodium cyanoborohydride reduction was attempted on the 2-pyrrolinone **191** as it was a less conjugated system. This reaction resulted in what appeared to be the saturated 2-pyrrolidinone **297** on analysis of the ^{1}H NMR spectrum of the crude material. On purification, the saturated compound was isolated in a 96% yield (Scheme 84).



Scheme 84: *Reduction of 2-pyrrolinone **191** to 2-pyrrolidinone **297***

The saturated 2-pyrrolidinone **297** was identified primarily in the ^{1}H NMR spectrum by the absence of alkene peaks at 7.18 ppm and 6.12 ppm that were assigned to the alkene across the C3−C4 carbons and the loss of the alkylidene proton at 5.37 ppm. There was no evidence of any alkene protons as all of the resonances were shifted

upfield into the aliphatic region of the spectrum. In this region of the ^{1}H NMR spectrum there were now three sets of diagnostic resonances. The first was a multiplet resonance integrating for a single proton at 3.39-3.49 ppm, which was assigned as the newly installed proton at C5 of the saturated 2-pyrrolidinone **297**. There was a multiplet integrating for two protons at 2.23-240 ppm, which was assigned as the protons at C3, while there were two multiplets integrating for a single proton each at 1.58-1.66 ppm and 2.05-2.14 ppm that were assigned as the diastereotopic protons at C4 (Figure 24).

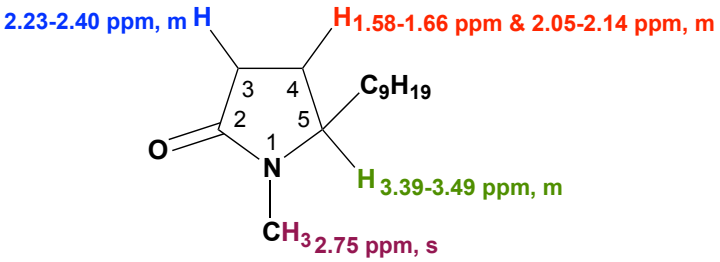
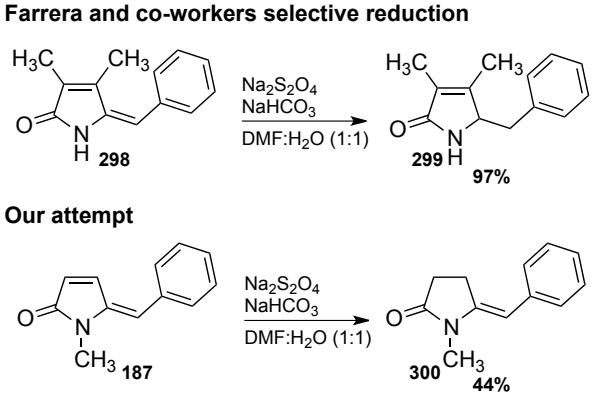


Figure 24: *Assignment of the diagnostic protons of saturated 2-pyrrolidinone* ***297***

The result of the reduction of 2-pyrrolinone **191** to 2-pyrrolidinone **297** was interesting and unprecedented in the literature, however, it was ultimately a dead-end product towards natural products like preussin. Compounds of this structure could be treated with a Grignard reagent such that alkylation or arylation could be possible at the C2 position, resulting in 1,2,5-trisubstituted pyrrolidines, however, this was not explored in the present study. In an attempt to promote selective reduction, the reaction conditions were modified such that 2-pyrrolinone **191** was dissolved in 20% acetic acid in dichloromethane, rather than neat acetic acid, before adding sodium cyanoborohydride. However, this again resulted in 2-pyrrolidinone **297**, albeit at a much slower rate. At this stage it was decided to move away from sodium cyanoborohydride and to investigate other reduction methodologies that could possibly reduce an enamine-like system.

The dissolving metal reduction of Zn in acetic acid is known to reduce enamines among other systems, however, its selectivity is not as reliable as hydride sources.[133] A solution of 2-pyrrolinone **187** and zinc metal in acetic acid was heated at reflux for 18 h. After this time however, analysis of the ^{1}H NMR spectrum of the crude material only provided evidence for the starting material with no reduced product being observed. While manipulations of compounds similar to 2-pyrrolinone **187** are

uncommon in the literature, there was an interesting report by Farrera and co-workers that involved the selective reduction that was desired on a structurally similar set of compounds (Scheme 83).[134] It was reported that 2-pyrrolinone **298** was selectively reduced at the alkylidene alkene, leaving the C3−C4 alkene in place, with a reducing system consisting of sodium dithionite and sodium hydrogen carbonate in DMF and water. Thus, 2-pyrrolinone **187** was treated under the reaction conditions as described by Ferrara. After 1 h at reflux, the starting material was consumed and as such was worked up to produce a crude reaction mixture that was purified to reveal alkylidene **300** in a 44% yield (Scheme 83).



Scheme 85: *The selective reduction methodology reported by Farrera and co-workers and the attempt at this reaction on pyrrolinone **187**.*

The alkylidene was primarily identified by analysis of the ^{1}H NMR spectrum, with the shift of the alkylidene proton from 6.46 ppm in the starting material to 5.77 ppm in the product. This upfield shift was a result of the alkene moving out of conjugation and becoming an isolated alkene. In the aliphatic region of the ^{1}H NMR spectrum there were now two signals, integrating for 2 protons each at 2.59 ppm and 3.01 ppm, which were not present in the starting material.

The reduction with sodium dithionite was exceptionally interesting as it gave the opposite chemoselectivity to that reported by Ferrera. This was likely a result of having a less hindered alkene at C3−C4, where as in all the examples reported by Ferrera the alkene was substituted with methyl groups at both positions, which would likely block access to the alkene due to steric effects. Again, in targeting such natural products as preussin this reduction was not useful due to the lack of an alkene across C3−C4. In a last attempt at selective reduction a catalytic hydrogenation of 2-

pyrrolinone **187** was investigated; however this resulted in the same product as was observed from the sodium dithionite reduction, albeit at a much slower rate.

After several attempts to find suitable reaction conditions for the selective reduction of the alkylidene alkene, no reaction conditions were identified. In saying this, some interesting reductions were briefly investigated leading to some novel compounds that could be significant in their own rights. However, the reductions that were able to proceed were seemingly substrate dependant. As such, trying to target densely functionalised pyrrolidinones or pyrrolidines starting from the oxidation of 2-substituted pyrroles with Dess−Martin periodinane did not appear to be a viable route for these compounds.

4.5 Conclusions and considerations for the future

The discovery the hypervalent iodine controlled oxidation of pyrrole was a significant and valuable reaction that led to densely functionalised 2-pyrrolinones. The LED photo-oxidation of pyrrole was a significant advancement on those reported photo-oxidations within the literature and it also led to the development of a photo-reactor that was amenable to a wide range of tasks. Both of these controlled methodologies were comprehensively studied in the previous two chapters contributing to breaking down the common misconception that using pyrrole under oxidative conditions leads to polypyrrole. Furthermore, both methodologies rapidly generate molecules that can be utilised within the total synthesis of a wide range of nitrogen containing, biologically significant, small molecules.

The present chapter detailed the conception of utilising 2-pyrrolinones as synthetic starting point in total synthesis. While the presently described methodologies ultimately did not perform as intended, some interesting chemistry was discovered and explored with a total synthesis of the natural product crispine A being a key achievement. Furthermore, the result of the methodologies within this chapter leads to different strategies and methodologies for utilising 2-pyrrolinones as key intermediates in targeted synthesis. It was clear that manipulation of the alkene at C3−C4 needed to occur before any other chemistry on the ring can occur. This methodology is presently being explored in a parallel study within the Smith research group.

Chapter 5 – Experimental

5.0 General Experimental

Nuclear Magnetic Resonance Spectroscopy

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectra were obtained on a Varian Mercury 2000 spectrometer operating at 300 MHz and 75 MHz respectively, or on a Bruker spectrometer operating at 400 MHz and 75 MHz respectively. Spectra were collected from samples dissolved in deuterated chloroform ($CDCl_3$), unless otherwise stated. Chemical shifts were recorded as δ values in parts per million (ppm) and referenced to the solvent used (in the case of $CDCl_3$, chemical shifts respectively appear at 7.26 ppm and 77.16 ppm for ^{1}H and ^{13}C spectra). Coupling constants were recorded in *J* values in Hz. The following abbreviations were used to describe ^{1}H spectra peak splitting patterns; s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, dq = doublet of quartets, bs = broad singlet and m = multiplet.

Infrared Spectroscopy

Infrared spectra were obtained on a Shimadzu FTIR 8400s spectrometer, using NaCl plates. Liquids and solids were recorded as thin films from either $CDCl_3$ or CH_2Cl_2 in cm^{-1}.

Mass Spectrometry

Mass spectrometry and High-Resolution mass spectrometry was performed on a Kratos Concept ISQ GC-MS instrument using electron impact mass spectrometry or by Liquid Secondary ion mass spectrometry with *m*-nitrobenzoic acid as the matrix; or by electrospray ionization by direct infusion into an LTQ-Orbitrap XL mass spectrometer using a syringe pump. Analytical analyses were performed by The Central Science Laboratory (CSL) at the University of Tasmania. The molecular ion and mass fragments are quoted, with relative intensities of the peaks referenced to the most intense taken as 100%.

Column Chromatography

Merck flash grade silica (32-63 μm) was used for column and flash chromatography, which was performed according to the general method of Still *et al*. Automated gradient flash chromatography was performed using a REVELERIS® X2 Flash Chromatography System provided by Grace Materials Technology. The system used 40 μm silica catridges.

Thin Layer Chromatography (TLC)

Merck silica gel 60 F254 aluminium backed sheets were used for analytical thin layer chromatography. TLC plates were visualised under a 254 nm UV lamp and/or by treatment with a phosphomolybdic acid (37.5 g), ceric sulfate (7.5 g), sulfuric acid (37.5 ml), water (720 ml) dip or a potassium permanganate dip (3 g $KMnO_4$, 20 g K_2CO_3, 5 ml 5% aqueous NaOH, 300 ml H_2O), followed by heating.

Solvents and Reagents

All solvents and reagents were purified by standard laboratory procedures. Anhydrous magnesium sulfate was used for drying organic extracts unless otherwise stated and solvents were removed under reduced pressure on a rotary evaporator.

Microwave assisted reactions

Microwave assisted reactions were conducted in heavy walled sealed tubes and heated using a CEM Discover Microwave reactor.

X-ray crystallography

The X-ray crystal structures reported herein are for X-ray diffraction data were collected at the Australian Synchrotron using the MX1 and MX2 (formerly PX1 and PX2) beamlines at −173 °C for crystals mounted on Hampton Scientific cryoloops. Data was collected on a single axis goniometer with 360 ° rotation at maximum resolution using the fixed detector. The Blu-Ice software package was employed to control the diffractometer and the data were reduced using XDS. All structures were solved by direct methods with SHELXS-97 and refined using full-matrix least-squares routines against F^2 with SHELXL-97, visualised using X-SEED. All non-hydrogen atoms were refined anisotropically and all hydrogens were placed

in calculated positions. Calculated hydrogens were refined using a riding model with fixed C−H distances of 0.95 (sp^2-CH), 0.99 (sp^3-CH, CH_2), 0.98 Å (CH_3). The thermal parameters of all calculated hydrogen atoms were estimated as $U_{iso}(H) = 1.2U_{eq}(C)$, except for CH_3- where $U_{iso}(H) = 1.5U_{eq}(C)$.

5.1 Miscellaneous Pyrrole synthesis

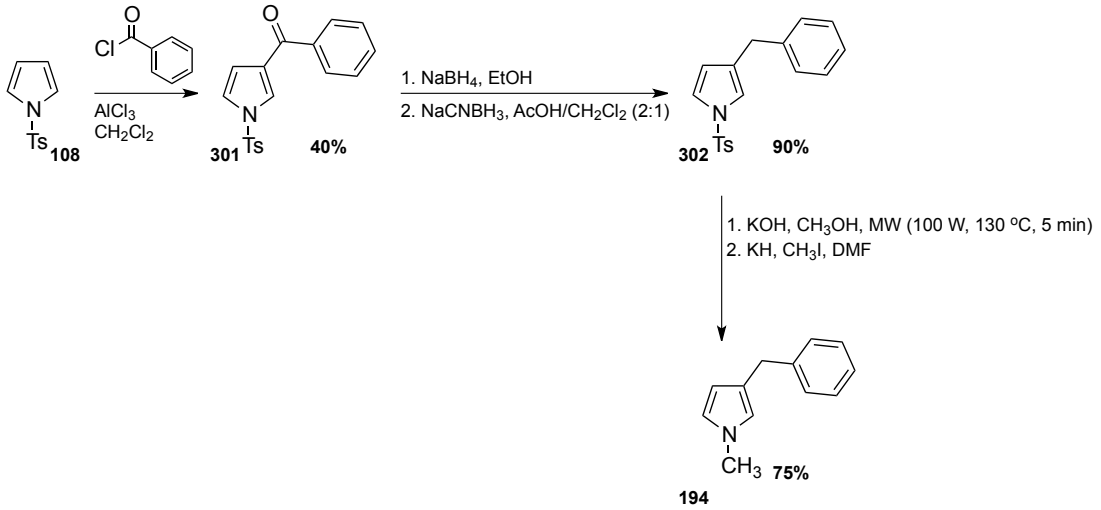
Methods for N-substituted pyrroles

N-Methylpyrrole (**118**) and *N*-ethylpyrrole (**169**) were both available commercially, however other pyrroles had to be synthesised in house. All *N*-alkyl pyrroles were synthesised following the general method of Gourlay *et al.*,[135] while *N*-aryl pyrroles were synthesised following the general method of Rivera *et al.*[135]

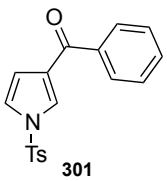
Methods for 2-substituted pyrroles

2-Benzyl-*N*-methylpyrrole (**185**), 2-ethyl-*N*-methylpyrrole (**188**) and *N*-methyl-2-nonylpyrrole (**190**) were all synthesised following the general method of Britttian *et al.*;[136] 2-Methyl-N-(*p*-methylbenzyl)pyrrole (**192**) was synthesised following the general method of Demir *et al.*;[137] Methyl-1-methyl-pyrrole-2-carboxylate (**180**) was synthesised following the method outlined in Smith *et al.*[138]

Method for 3-benzyl-N-methylpyrrole (193)



Phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]formaldehyde (301)

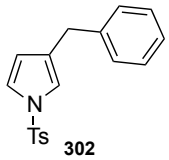


To a dry flask under a nitrogen atmosphere loaded with 1-(*p*-tolylsulfonyl)-pyrrole (**108**) (2.00 g, 9.02 mmol) and $AlCl_3$ (1.51 g, 11.3 mmol) was added CH_2Cl_2 (20.0

mL), resulting in a deep red reaction mixture. A solution of benzoyl chloride (1.52 g, 1.26 mL, 10.8 mmol) in CH_2Cl_2 (5 mL) was slowly added to the primary reaction mixture over 5 mins. The reaction mixture was stirred for 2 h before being quenched by addition of the reaction mixture to an ice slurry. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with $NaHCO_3$ (2 × 15 mL), dried on $MgSO_4$ and filtered. The solvent was removed by evaporation under reduced pressure to yield a crude mixture, with phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]formaldehyde (**301**) being isolated by flash chromatography on silica gel elution with 20% ethyl acetate: hexanes in a 40% yield (1.18 g, 3.62 mmol) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 6.79 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.20 (dd, *J* = 3.3, 2.1 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.45-7.61 (m, 3H), 7.64 (t, *J* = 1.5 Hz, 1H), 7.80-7.66 (m, 2H), 8.14-8.11 (m, 2H).

Phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]methane (302)



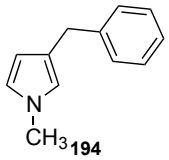
302

Phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]formaldehyde (**301**) (703 mg, 2.16 mmol) was dissolved in EtOH (25 mL). The reaction mixture was cooled to 0 °C before the addition of $NaBH_4$ (172 mg, 4.57 mmol) and was stirred for 2 h. After this time H_2O (30 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with H_2O (50 mL), dried on $MgSO_4$ and filtered. The solvent was removed by evaporation under reduced pressure to yield phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]methanol (**303**), which was subsequently used in the next step without further purification. Phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]methanol was dissolved in CH_2Cl_2 (10 mL) before adding AcOH (20 mL) and cooling to 0 °C. To the reaction mixture was added $NaCNBH_3$ (243 mg, 3.88 mmol) and the resultant mixture was stirred for 18 h. After this time it was apparent that the reduction was not complete, so additional $NaCNBH_3$ (246 mg, 3.92 mmol) was added and the reaction mixture was heated to 40 °C for 5 h. After this time the reaction mixture was cooled and had the solvent removed by evaporation under reduced pressure. The

crude residue was taken up in CH_2Cl_2 (20 mL) and H_2O (50 mL), the organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The organic fractions were combined and washed with H_2O (2 × 40 mL), dried on $MgSO_4$ and filtered before the solvent was removed by evaporation under reduced pressure resulting in phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]methane (**302**) in a 90% yield (546 mg, 1.75 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.76 (s, 2H), 6.14 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.94 (s, 1H), 7.11 (dd, *J* = 3.2, 2.4 Hz, 1H), 7.31-7.10 (m, 7H), 7.75 (d, *J* = 8.7 Hz, 2H).

Phenyl(1-methyl-pyrrol-3-yl)methane (194)



194

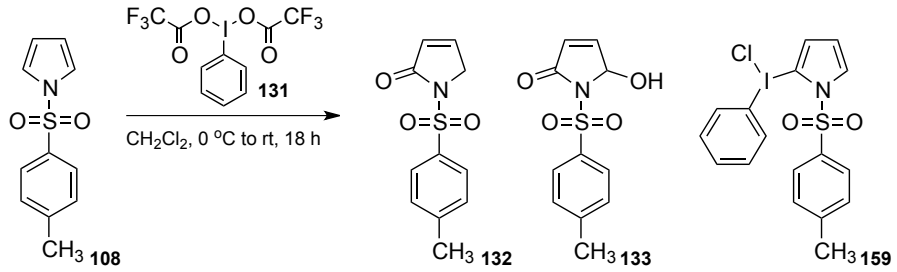
Crude phenyl[1-(*p*-tolylsulfonyl)-pyrrol-3-yl]methane (**302**) (50.0 mg, 0.16 mmol) was taken in CH_3OH (4 mL) with KOH (93.6 mg, 1.66 mmol) and heated at 130 °C for 5 mins in a microwave (130 W). After cooling to room temperature the reaction mixture was dissolved in CH_2Cl_2 (10 mL) and H_2O (20 mL), before the organic portion was removed and the aqueous portion extracted further with CH_2Cl_2 (2 × 10 mL). The organic fractions were combined and washed with H_2O (30 mL), dried on Na_2SO_4 and filtered before the solvent was removed by evaporation under reduced pressure to yield phenyl(*1H*-pyrrol-3-yl)methane (**304**) in 75% (17.6 mg, 0.12 mmol). Phenyl(*1H*-pyrrol-3-yl)methane (**304**) and CH_3I (20 μL, 45.6 mg, 0.32 mmol) was dissolved in dry DMF (1 mL) before cooling to 0 °C. To the cooled mixture was added KH (40 mg, 1.0 mmol) and the reaction mixture was stirred for 2 h. After this time, H_2O (10 mL) was slowly added and the reaction mixture was extracted with a 1:1 mixture of ethyl acetate/ hexanes (4 × 10 mL). The combined organic fractions were collected and washed with H_2O (2 × 10 mL), dried on $MgSO_4$ and filtered before the volatiles were removed by evaporation under reduced pressure. Phenyl(1-methyl-pyrrol-3-yl)methane (**194**) (21. 0 mg, 0.12 mmol) was

obtained in a 99% yield as an orange oil that was clean enough for further reactions without further purifications.

^{1}H NMR (400 MHz, $CDCl_3$) δ	3.63 (s, 3H), 3.87 (s, 2H), 6.02 (t, *J* = 2.4 Hz, 1H), 6.38 (s, 1H), 6.55 (t, *J* = 2.4 Hz, 1H), 7.21-7.35 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	33.6, 36.1, 108.7, 119.9, 121.8, 123.5, 125.7, 128.3, 128.7, 142.5.

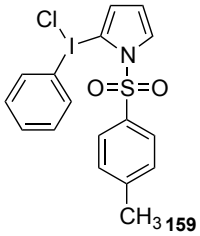
5.2 Chapter 2 Experimental

Oxidation of N-tosylpyrrole with PIFA



To a solution of PIFA (**131**) (364 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) was added *N*-tosylpyrrole (**108**) (102 mg, 0.46 mmol) at 0 °C. The mixture stirred for 18 h before the addition of water (10 mL) and solid $Na_2S_2O_5$. The resulting solution was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with a solution of saturated aqueous $NaHCO_3$ (2 × 10 mL), saturated aqueous NaCl (20 mL) and dried on $MgSO_4$. Solvent was evaporated under reduced pressure to yield the crude mixture. Isolation of the mixed 2-pyrrolinones **132** and **133** was performed by flash chromatography on silica gel with gradient elution of 20% ethyl acetate/hexanes to 60% ethyl acetate/hexanes. Isolation of 2-(chlorophenyliodo)-1-(*p*-tolylsulfonyl)-1*H*-pyrrole (**159**) was performed with 100% ethyl acetate in 24% yield (53 mg, 0.11 mmol). ^{1}H NMR data obtained for the 2-pyrrolinones matched that reported by Alp *et al.*[78]

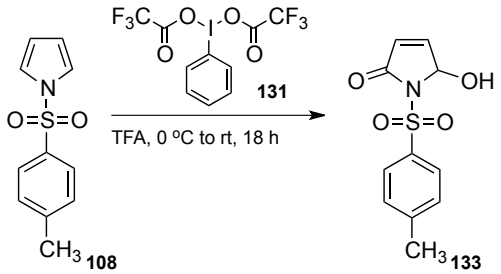
2-(Chlorophenyliodo)-1-(*p*-tolylsulfonyl)-1*H*-pyrrole (159)



159

IR (thin film)	3121, 3056, 2925, 1661, 1373, 1083 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$) δ	2.37 (s, 3H), 6.40 (t, *J* = 3.6 Hz, 1H), 6.86 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* =8.0 Hz, 2H), 7.45 (dd, *J* = 3.6,1.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.0, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	21.8, 94.5, 115.6, 121.3, 127.5, 128.6, 129.5, 130.7, 131.82, 131.85, 133.9, 134.3, 146.7.
MS (+EI) *m/z*	423 (M −Cl, 5), 347 (32), 204 (35), 155 (56), 91 (100).

***RS*-5-hydroxy-1-(*p*-tolylsulfonyl)-pyrrol-2-one (133)**



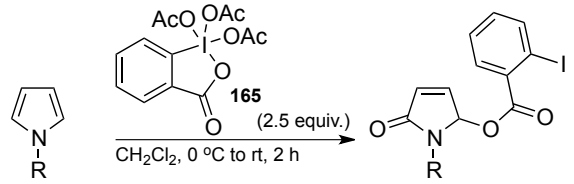
108 **133**

A solution of *N*-tosylpyrrole (**108**) (0.51 g, 2.32 mmol) in TFA (10 mL) was cooled to 0 °C before the slow addition of PIFA (**131**) (2.17 g, 5.05 mmol). This mixture stirred over 18 h while warming to room temperature. After this time water was added to the reaction mixture followed by solid $Na_2S_2O_5$. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with $NaHCO_3$ (2 × 20 mL) and dried on $MgSO_4$. The solution was filtered before removal of the solvent by evaporation under reduced pressure to yield the crude material that was purified by flash chromatography on silica gel with 70% ethyl acetate to yield 5-Hydroxy-1-(*p*-

tolylsulfonyl)-pyrrol-2-one (**133**) in 63% (0.37 g, 1.46 mmol). ^{1}H NMR and ^{13}C NMR data collected were identical to that reported by Alp *et al.*[78]

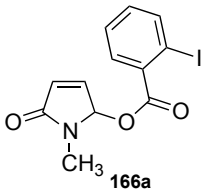
^{1}H NMR (300 MHz, $CDCl_3$) δ	2.44 (s, 3H), 6.06 (d, *J* = 6.0 Hz, 1H), 6.22 (s, 1H), 7.07 (dd, *J* = 6.0, 1.8 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	21.8, 83.4, 127.8, 128.2, 129.9, 135.4, 145.5, 147.6, 166.3.

General experimental for Dess−Martin Periodinane oxidation of pyrroles.



To a solution of Dess−Martin periodinane (**165**) (2.5 equiv.) in CH_2Cl_2 (0.1M) at 0 °C was slowly added *N*-alkyl pyrrole (1.0 equiv.). The reaction mixture was stirred at 0 °C for 2 h before adding H_2O and quenching with solid $Na_2S_2O_5$. The resulting solution was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with a solution of saturated $NaHCO_3$ (3 x 10 mL) before drying on Na_2SO_4 and filtered. Solvent was evaporated under reduced pressure to yield the crude product, before purification by flash chromatography on silica gel.

***RS*-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate (166a)**



166a

From *N*-methylpyrrole (**118**) following the general method in 81% yield, isolated as a yellow oil after purification with 40% ethyl acetate: hexanes.

IR (thin film)	3094, 2926, 1718, 1582, 1244, 1014 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ	3.01 (s, 3H), 6.30 (d, *J* = 6.0 Hz, 1H), 6.65 (s, 1H), 7.09 (dd, *J* = 6.0, 1.8 Hz, 1H), 7.18 (td, *J*

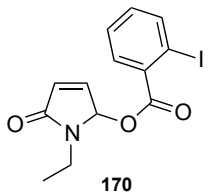
= 7.8, 1.8 Hz, 1H), 7.40 (td, *J* = 8.1, 1.2 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.00 (dd, *J* = 8.1, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ — 27.3, 85.4, 94.6, 128.3, 130.5, 131.5, 133.6, 133.7, 141.9 (2 × overlapping resonances), 165.9, 170.1.

MS (+EI) *m/z* — 343 (M+, 1).

HRMS (+EI) *m/z* — for $C_{12}H_{10}INO_3$ calc. 342.97053, found 342.97024.

_RS_-1-ethyl-5-oxo-pyrrol-2-yl _o_-iodobenzoate (170)



170

From *N*-ethylpyrrole (**169**) following the general method in a 83% yield. The title compound was isolated as a yellow semisolid after purification with 40% ethyl acetate: hexanes.

IR(thin film) — 3094, 2974, 1723, 1582, 1223, 1014 cm^{-1}.

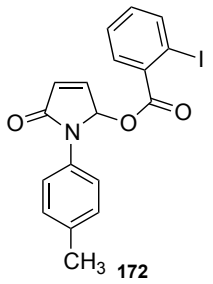
^{1}H NMR (300 MHz, $CDCl_3$) δ — 1.20 (t, *J* = 7.2 Hz, 3H), 3.31 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.69 (dq, *J* = 14.2, 7.1 Hz, 1H), 6.28 (d, *J* = 6 Hz, 1H), 6.76 (d, *J* = 1.5 Hz, 1H), 7.09 (dd, *J* = 6, 1.8 Hz), 7.18 (td, *J* = 7.2, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.2 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.01 (dd, *J* = 7.8, 0.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ — 14.0, 35.3, 83.7, 94.6, 128.3, 130.5, 131.5, 133.5, 133.6, 141.9 (2 × overlapping resonances), 165.8, 169.8.

MS (+EI) *m/z* — 357 (M+, 100), 230 (47).

HRMS (+EI) *m/z* — for $C_{13}H_{12}INO_3$ calc. 356.9861, found 356.9935.

***RS*-1-(*p*-methylphenyl)-5-oxo-pyrrol-2-yl *o*-iodobenzoate (172)**

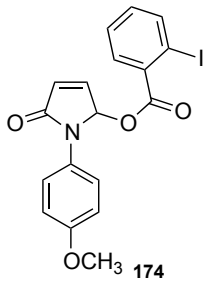


172

From *N*-(p-methylphenyl)pyrrole (**171**) following a modified general method, where extraction was preformed with ethyl acetate (3 x 10 mL) before the combined organic extracts were washed with a solution of saturated $NaHCO_3$ (3 x 10 mL), dried on Na_2SO_4 and filtered. The title compound was isolated in an 88% yield as a yellow oil after purification with 30% ethyl: hexanes.

IR (thin film)	2923, 1718, 1581, 1516, 1205, 1014 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	2.32 (s, 3H), 6.42 (d, *J* = 6.0 Hz, 1H), 7.11-7.17 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.22-7.28 (m, 2H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.62 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.98 (dd, *J* = 7.9, 1.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	21.2, 84.3, 94.6, 122.6, 128.2, 130.1, 130.8, 131.5, 133.3, 133.6, 136.0, 141.7, 141.8, 165.6, 168.8.
MS (+EI) *m/z*	419 (M+, 12), 172 (100).
HRMS (+EI) *m/z*	for $C_{18}H_{14}INO_3$ calc. 419.00184, found 419.00271.

***RS*-1-(*p*-methoxyphenyl)-5-oxo-pyrrol-2-yl *o*-iodobenzoate (174)**



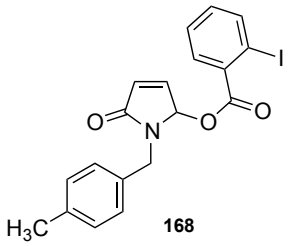
174

From *N*-(*p*-methoxylphenyl)pyrrole (**173**) following a modified general method, where extraction was preformed with ethyl acetate (3 x 10 mL) before the combined

organic extracts were washed with a solution of saturated $NaHCO_3$ (3 x 10 mL), dried on Na_2SO_4 and filtered. The title compound was isolated in a 93% yield as a yellow oil after purification with 30% ethyl: hexanes.

IR (thin film)	2932, 1715, 1582, 1513, 1393, 1248, 1209, 1014 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	3.72 (s, 3H), 6.36 (d, *J* = 5.9 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.08 (td, *J* = 7.8, 1.7 Hz, 1H), 7.12-7.19 (m, 2H), 7.24-7.29 (m, 1H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.56 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.2 Hz, 1H).
^{13}C NMR (75 MHz, CDCl3) δ	55.7, 84.7, 94.6, 114.8, 125.5, 128.3, 130.8, 131.5, 133.6, 141.8, 141.9, 158.1, 165.6, 169.0, 170.4.
MS (+EI) *m/z*	435 (M+, 18), 188 (100).
HRMS (+EI) *m/z*	for $C_{18}H_{14}INO_4$ calc. 434.99675, found 435.99791.

***RS*-1-(*p*-methylbenzyl)-5-oxo-pyrrol-2-yl *o*-iodobenzoate (168)**



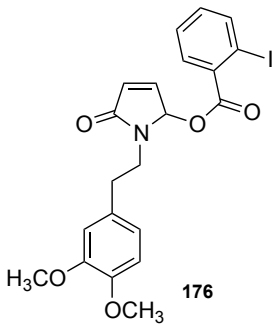
168

From *N*-(*p*-methylbenzyl)pyrrole (**167**) following the general method in 93% yield. The title compound was isolated as a brown semisolid after purification with 50% ethyl acetate: hexanes. Crystals were collected after the slow evaporation of $CHCl_3$ from a saturated solution of **168**.

IR (thin film)	2924, 1718, 1582, 1244, 1014 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	2.27 (s, 3H), 4.44 (d, *J* = 15.0 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 6.35 (d, *J* = 6 .0 Hz, 1H), 6.64 (d, *J* = 1.5 Hz, 1H), 7.06 (s, 1H), 7.08-7.10 (m, 2H), 7.15-7.18 (m, 2H), 7.32 (td, *J* = 7.8,

	1.2 Hz, 1H), 7.44 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	21.3, 44.1, 83.9, 94.6, 128.1, 128.4, 129.6, 130.2, 131.5, 133.5, 133.8, 137.5, 141.8, 142.3, 165.5, 170.0.
MS (+EI) *m/z*	433 (M+, 2), 248 (47), 202 (17).
HRMS (+EI) *m/z*	for $C_{19}H_{16}INO_3$, calc. 433.01748, found 433.01876.

_RS_-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-oxo-pyrrol-2-yl *o*-iodobenzoate (176)



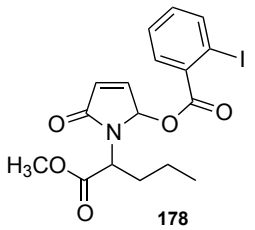
176

From *N*-[2-(3,4-Dimethoxyphenyl)ethyl]pyrrole (**175**) following the general method in 96% yield. The title compound was isolated as brown oil after purification with 50% ethyl acetate: hexanes.

IR(thin film)	2938, 2833, 1715, 1582, 1263, 1014 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ	2.84 (ddd, *J* = 13.5, 8.9, 6.4 Hz, 1H), 2.94 (ddd, *J* = 13.7, 9.0, 6.2 Hz, 1H), 3.44 (ddd, *J* = 14.2, 8.9, 6.2 Hz, 1H), 3.83 (s, 2H), 3.84 (s, 3H), 3.92 (ddd, *J* = 14.3, 9.0, 6.4 Hz, 1H), 6.30 (dd, *J* = 5.9, 0.7 Hz, 1H), 6.63 (d, *J* = 1.7 Hz, 1H), 7.05 (dd, *J* = 5.9, 1.8 Hz, 1H), 7.20 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.8, 7.5, 1.2 Hz, 1H), 7.77 (ddd, *J* = 7.8, 1.5, 0.3 Hz, 1H), 8.03 (ddd, *J* = 8.1, 1.2, 0.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ	34.3, 42.1, 56.0, 56.1, 84.0, 94.6, 111.4, 112.1, 120.9, 128.3, 130.4, 130.9, 131.5, 133.7, 142.0, 142.1, 147.8, 149.1, 165.8, 170.1.
MS (+EI) *m/z*	493 (M+, 7), 261 (32), 248 (19).
HRMS (+EI) *m/z*	for $C_{21}H_{20}INO_5$, calc. 493.03861, found 493.03919.

_RS_-1-(1-methoxycarbonylbutyl)-5-oxo-pyrrol-2-yl _o_-iodobenzoate (178)

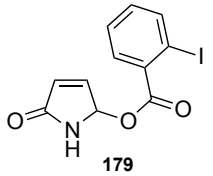


178

From the racemic mixture of 1-(1-methoxycarbonylbutyl)pyrrole (**177**) following the general method in 86% yield. The title compound was isolated as a brown oil in a 1:1 mixture of diastereomers, after purification with 30% ethyl acetate: hexanes.

^{1}H NMR (300 MHz, $CDCl_3$) δ	0.83 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 1.39 (dddd, *J* = 20.7, 13.9, 9.8, 5.0 Hz, 4H), 1.78-2.09 (m, 4H), 3.61 (s, 3H), 3.73 (s, 3H), 4.59 (dd, *J* = 9.4, 6.3 Hz, 1H), 4.80 (dd, *J* = 10.7, 5.2 Hz, 1H), 6.33 (dd, *J* = 6.0, 2.2 Hz, 1H), 6.75-6.81 (m, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 7.14-7.23 (m, 3H), 7.41 (ddd, *J* = 5.4, 4.5, 2.2 Hz, 2H), 7.80 (ddd, *J* = 9.6, 7.8, 1.7 Hz, 2H), 8.03 (dd, *J* = 7.9, 2.9 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	13.6, 13.7, 19.6, 19.7, 30.7, 31.9, 52.5, 52.6, 54.2, 54.3, 83.3, 84.8, 94.6, 94.7, 128.2, 128.8, 129.1, 129.8, 131.3, 131.5, 133.2, 133.60, 133.61, 141.9, 142.0, 142.9, 143.5, 143.6, 165.3, 165.5, 170.5, 171.3, 171.5, 171.7.
MS (+EI) *m/z*	443 (M+, 7), 248 (14), 212 (17).
HRMS (+EI) *m/z*	for $C_{17}H_{18}INO_5$, calc. 443.02296, found 443.02342.

***RS*-5-oxo-pyrrol-2-yl *o*-iodobenzoate (179)**

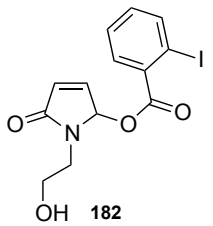


179

From pyrrole (**81**) following the general method in 56% yield. The title compound was isolated as a brown oil without need for further purification.

IR (thin film)	3246, 3103, 1719, 1582, 1247, 1015 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	6.28-6.33 (m, 1H), 6.54-6.57 (m, 1H), 6.67 (bs, 1H), 7.11-7.23 (m, 2H), 7.43 (td, *J* = 7.4, 3.9 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.03 (dd, *J* = 7.4, 0.6 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	81.3, 94.7, 128.3, 130.4, 131.7, 133.8, 142.0, 144.2, 166.4, 171.9.
MS (+EI) *m/z*	329 (M+, 100), 230(88).
HRMS (+EI) *m/z*	for $C_{11}H_8INO_3$, calc. 329.9548, found 329.9622.

***RS*-1-(2-hydroxylethyl)-5-oxo-pyrrol-2-yl *o*-iodobenzoate (182)**



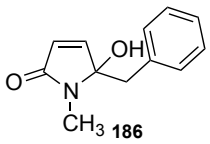
182

From *N*-(2-hydroxylethyl)pyrrole (**181**) following a modified general method, where 1 equivalent of Dess−Martin periodinane (**165**) was used instead of 2.5 equivalents. The title compound was isolated in 61% yield as a colourless oil after purification with 60% ethyl acetate: hexanes.

IR (thin film)	3403, 2935, 2879, 1681, 1582, 1413, 1245, 1089 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	3.05 (bs, 1H), 3.42-3.51 (m, 1H), 3.70-3.80 (m, 3H), 6.28 (d, *J* = 6 Hz, 1H), 6.83 (s, 1H), 7.10-7.18 (m, 2H), 7.39 (dt, *J* = 7.8, 1.2 Hz, 1H),

	7.79 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.97 (dd, *J* = 8.1, 1.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	43.5, 61.1, 84.8, 94.4, 128.1, 129.9, 131.3, 133.3, 133.5, 141.6, 142.5, 165.7, 170.9.
MS (+EI) *m/z*	395 (M+Na, 75), 270 (10).
HRMS (+EI) *m/z*	for $C_{13}H_{12}INNaO_4$, calc. 395.9709, found 395.9704.

_RS_-5-benzyl-5-hydroxy-1-methyl-pyrrol-2-one (186)

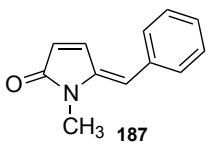


186

From 2-benzyl-*N*-methylpyrrole (**185**) following the general method in 35% yield. The title compound was isolated after purification with 100% ethyl acetate.

IR (thin film)	3314, 3027, 2925, 1701, 1596 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ	2.88 (d, *J* =13.7 Hz, 1H), 2.90 (s, 1H), 3.24 (d, *J* = 13.7 Hz, 1H), 5.86 (d, *J* = 6.0 Hz, 1H), 6.81 (d, *J* = 6.0 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.21-7.30 (m, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	23.8, 42.1, 92.0, 126.9, 127.3, 128.5, 130.2, 134.9, 149.2, 169.6.
MS (+EI) *m/z*	226 (M+Na, 100), 204 (22), 186 (18).
HRMS (+EI) *m/z*	for $C_{12}H_{13}NO_2Na$, calc. 226.0844, found 226.0839.

(_E_)-5-Phenylmethylidene-1-methyl-pyrrol-2-one (187)



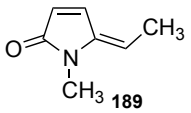
187

From 2-benzyl-*N*-methylpyrrole (**185**) following the general method. After the initial workup, the crude mixture (99.9 mg) was reacted under nitrogen with BF_3•OEt_2 (86.2 mg, 0.60 mmol) and Et_3SiH (72.8 mg, 0.63 mmol) in CH_2Cl_2 (4 mL) for 20 h. The reaction mixture was quenched with saturated K_2CO_3 and extracted with CH_2Cl_2 (3 x 5 mL). The organic fractions were collected, dried on Na_2SO_4 and filtered before

the solvent was removed under reduced pressure. The crude mixture was purified on silica with 40% ethyl acetate:hexanes to reveal the title compound as a brown semi solid in a 2 step 89% yield (74.1 mg, 0.40 mmol).

IR (thin film)	3058, 2945, 1691, 1632, 1432, 1122 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	3.21 (s, 3H), 6.27 (dd, *J* = 5.9, 1.7 Hz, 1H), 6.42 (s, 1H), 7.45-7.26 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	25.6, 113.7, 125.7, 127.9, 128.8, 129.3. 133.9, 134.9, 141.1, 169.8.
MS (+EI) *m/z*	185 (M+, 100), 156 (78), 129 (18), 115 (29).
HRMS (+EI) *m/z*	for $C_{12}H_{11}NO$, calc. 185.08406, found 185.08411.

(*E*)-5-Ethylidene-1-methyl-pyrrol-2-one (189)

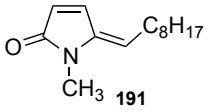


189

Following the procedure for (*E*)-5-phenylmethylidene-1-methyl-pyrrol-2-one (**187**); from 2-ethyl-*N*-methylpyrrole (**188**) in 96% yield, the title compound was isolated as an orange oil after purification with 30% ethyl acetate: hexanes.

IR (thin film)	2978, 2890, 1643, 1434, 809 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$) δ	1.97 (d, *J* = 7.5 Hz, 3H), 3.09 (s, 3H), 5.45 (q, *J* = 7.5 Hz, 1H), 6.18 (d, *J* = 5.9 Hz, 1H), 7.25 (d, *J* = 5.9 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	13.1, 25.4, 109.7, 124.5, 131.8, 141.3, 170.2.
MS (+EI) *m/z*	123 (M+, 100), 94 (49).

(*E*)-5-Nonylidene-1-methyl-pyrrol-2-one (191)



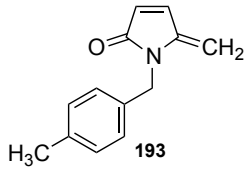
191

Following the procedure for (*E*)-5-Phenylmethylidene-1-methyl-pyrrol-2-one (**187**); from *N*-methyl-2-nonylpyrrole (**190**) in 99% yield, the title compound was isolated as an orange oil after purification with 30% ethyl acetate: hexanes.

IR (thin film)	2925, 2854, 1695, 1431 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ	0.86 (t, *J* = 7.4 Hz, 3H), 1.35-1.17 (m, 10H), 1.50-1.42 (m, 2 H), 2.31 (q, *J* = 7.4 Hz, 2H), 3.08 (s, 3H), 5.38 (t, *J* =8.0 Hz, 1H), 6.14 (d, *J* = 6.0 Hz, 1H), 7.20 (d, *J* = 6.0 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	14.1, 22.7, 25.3, 27.6, 29.2, 29.3, 29.4, 30.3, 31.9, 115.3, 124.4, 132.1, 140.7, 170.1.
MS (+EI) *m/z*	221(M+, 3), 122 (47), 113 (100).
HRMS (+EI) *m/z*	for $C_{14}H_{23}NO$, calc. 221.17796, found 221.17796.

5-Methylene-1-(*p*-methylbenzyl)-pyrrol-2-one (193)

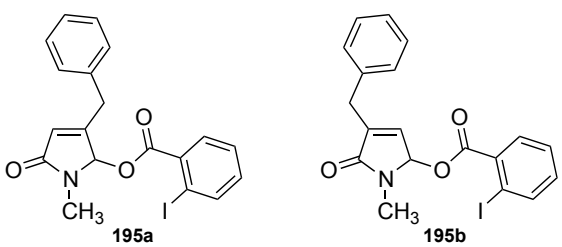


193

Following the procedure for (*E*)-5-phenylmethylidene-1-methyl-pyrrol-2-one (**187**); from *N*-(*p*-methylbenzyl)-2-methylpyrrole (**192**) in 99% yield, the tilte compound was isolated as an off white semi solid after purification with 30% ethyl acetate: hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ	2.33 (s, 3H), 4.82-4.80 (m, 3H), 4.85 (t, *J* = 1.6Hz, 1H), 6.27 (dd, *J* = 5.8, 0.8 Hz, 1H), 7.00 (d, *J* = 5.8 Hz, 1H), 7.12 (s, 4H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	21.1, 42.5, 97.7, 125.0, 127.0, 129.4, 134.1, 137.0, 137.5, 145.2, 170.5.
MS (+EI) *m/z*	199 (M+, 11), 120 (30), 105 (100)
HRMS (+EI) *m/z*	for $C_{13}H_{13}NO$, calc. 199.09971, found 199.09929.

***RS*-4-Benzyl-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate + *RS*-3-Benzyl-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate (195a + 195b)**

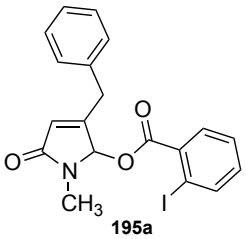


195a

195b

From 3-benzyl-*N*-methylpyrrole (**194**) following the general method in a combined yield of 61%. The title compounds were isolated on silica with 30% ethyl acetate: hexanes to reveal a 36% yield of 3-benzyl-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate (**195a**) and 25% yield of 4-benzyl-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate (**195b**).

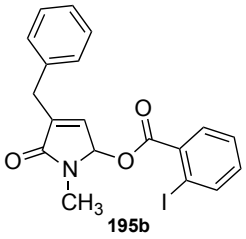
_RS_-3-benzyl-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate (195a)



195a

IR (thin film)	3062, 2924, 1711, 1582, 1240, 1014 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ	2.97 (s, 3H), 3.69 (dd, *J* = 31.7, 17.3 Hz, 2H), 5.89 (s, 1H), 6.66 (s, 1H), 7.33-7.15 (m, 6H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	27.3, 34.8, 84.8, 94.6, 125.2, 127.2, 128.2, 129.05, 129.08, 129.2, 131.3, 133.5, 136.0, 141.8, 157.3, 165.9, 170.2.
MS (+EI) *m/z*	433 (M+, 5), 186 (100).
HRMS (+EI) *m/z*	for $C_{19}H_{16}INO_3$ calc. 433.01746, found 433.01784.

_RS_-4-benzyl-1-methyl-5-oxo-pyrrol-2-yl *o*-iodobenzoate (195b)

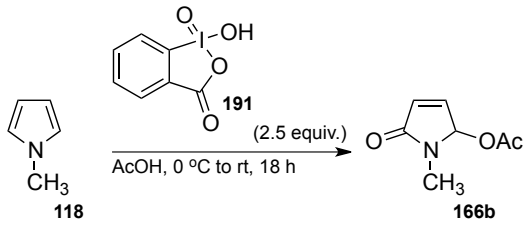


195b

IR (thin film)	3062, 2925, 1712, 1581, 1242, 1013 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ	3.05 (s, 3H), 3.64 (s, 2H), 6.49 (d, *J* = 3.0 Hz, 1H), 6.54 (s, 1H), 7.18 (dt, *J* = 8.1, 1.5 Hz, 1H), 7.21-7.26 (m, 5 H), 7.41 (t, *J* = 9.0 Hz), 7.79 (dd, *J* = 9.0, 3.0 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	27.6, 32.2, 84.2, 94.4, 126.8, 128.2, 128.8, 129.2, 131.4, 133.4, 133.8, 134.7, 137.3, 141.8, 143.1, 166.0, 170.2.
MS (+EI) *m/z*	433 (M+, 10), 341 (4), 306 (3), 185 (100).
HRMS (+EI) *m/z*	for $C_{19}H_{16}INO_3$ calc. 433.01746, found 433.01574.

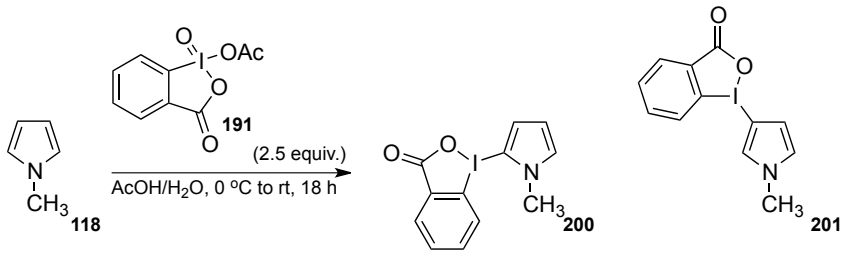
The oxidation of *N*-methylpyrrole (118) with IBX (191)



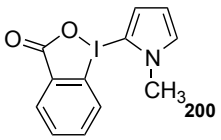
To a solution of IBX (**191**)(4.5 g, 16 mmol) in neat acetic acid (40 mL) was slowly added *N*-methylpyrrole (**118**)(500 mg, 6.1 mmol) at 0 °C. The reaction mixture was stirred for 18 h before the addition of H_2O followed by dry NaS_2O_5. The resultant mixture was made alkaline with a solution of saturated $NaCO_3$ before extracting with CH_2Cl_2 (3 x 10 mL). The organic fractions were collected before drying on $MgSO_4$. Solvent was removed under reduced pressure to yield *RS*-5-acetoxyl-2-pyrrolinone **166b** (838 mg, 5.4 mmol) in 88%. ^{1}H NMR spectrum collected matched the data provided by Feringa e*t al.*[139]

^{1}H NMR (400 MHz, $CDCl_3$) δ	2.15 (s, 3H), 2.92 (s, 3H), 6.25 (d, *J* = 6.1 Hz, 1H), 6.41 (d, *J* = 1.6 Hz, 1H), 6.94 (dd, *J* = 6.1, 1.6 Hz, 1H).

The synthesis of 2-iodiniumpyrrole 200 and 3-iodoniumpyrrole 201

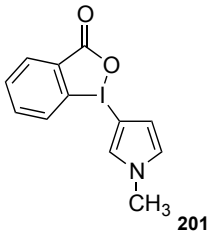


To a solution of IBX (**191**) (3.63 g, 13 mmol) in 50% acetic acid/H_2O (20 mL) was slowly added *N*-methylpyrrole (500 mg, 6.1 mmol). The reaction mixture stirred for 20 h before quenching on addition of dry NaS_2O_5. The mixture was diluted further with H_20 (~50 mL) before extracting with CH_2Cl_2 (3 ×15 mL). The organic extracts were washed carefully with a solution of saturated $NaHCO_3$ (2 × 20 mL) before drying on $MgSO_4$. Solvent was removed under reduced to yield the crude mixture in a combined 46% yield, which was purified for analysis by the Reveleris® flash chromatography system on an elution gradient of 100% ethyl acetate to 20% methanol/ethyl acetate. After purification 2-iodoniumpyrrole **200** (107 mg, 0.32 mmol) was obtained in an 5% yield as a dark oil, while 3-iodoniumpyrrole **201** (80 mg, 0.24 mmol) was obtained in a 4% yield brown semi solid that was recrystallised from ether/hexanes.



IR (thin film)	3441, 3106, 2945, 1605, 1557, 1345, 1287.
^{1}H NMR (400 MHz, $CDCl_3$) δ	3.75 (s, 3H), 6.41 (dd, *J* = 3.8, 2.8 Hz, 1H), 6.63 (d, *J* = 8.2, 1H), 6.89 (dd, *J* = 3.8, 1.6 Hz, 1H), 7.07 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.46 (dt, *J* = 7.2, 2.0 Hz, 1H), 7.59 (dt, *J* = 7.2, 0.8 Hz, 1H), 8.39 (dd, *J* = 7.2, 1.6 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	37.4, 96.6, 112.1, 118.9, 125.1, 125.3, 129.7, 130.9, 132.7, 133.0, 134.0, 166.9.
MS (+EI) *m/z*	327 (M+, 10), 207 (100), 105 (15), 39 (22).

HRMS (+EI) *m/z* for $C_{12}H_{10}INO_2$ calc. 326.97562, found 326.97601.



201

IR (thin film) 3441, 3108, 2950, 1605, 1557, 1359.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.48 (dd, *J* = 2.8, 1.6 Hz, 1H), 6.83 (t, *J* =2.3 Hz, 1H), 6.83 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.00 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.17 (t, *J* = 1.8 Hz, 1H), 7.42 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.53 (dt, *J* =7.2, 0.8 Hz, 1H), 8.36 (dd, *J* = 7.2, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0, 83.7, 115.7, 116.9, 125.6, 126.1, 130.3, 131.3, 132.3, 133.0, 133.3, 167.0.

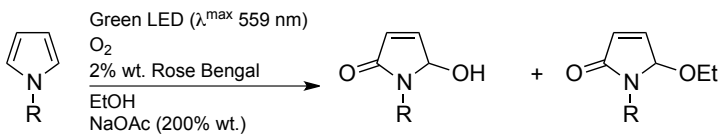
MS (+EI) *m/z* 327 (M+, 5), 207 (100), 105 (15), 39 (15).

HRMS (+EI) *m/z* for $C_{12}H_{10}INO_2$ calc. 326.97562, found 326.97510.

5.3 Experimental for Chapter 3

The general photo-reactor design is outlined in Chapter 3. The following sections consist of experimental data and procedures only.

General experimental for the Photo-oxidation of pyrroles.



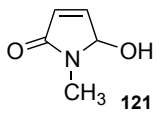
Into the green LED photo-reactor was added Rose Bengal (**211**) (~2% wt./wt.), NaOAc (~100-200% wt./wt. saturated aqueous solution), EtOH (70 mL), followed by the addition of pyrrole (100-500 mg). The resultant solution was then submerged

in an ice/water bath and had a stream of O_2 bubbled through it before light was turned on. The solution was irradiated for 0.5-2 h before the light was turned off and the solvent evaporated. The crude mixture was flushed through a plug of silica gel to yield a mixture of the 5-hydroxy-pyrrol-2-one and the 5-ethoxy-pyrrol-2-one. The resulting mixture was purified on a Reveleris® X2 Automated flash chromatography unit.

_RS_-5-hydroxy-1-methyl-pyrrol-2-one (121) + _RS_-5-ethoxy-1-methyl-pyrrol-2-one (243)

Following the general procedure; using *N*-methylpyrrole(**118**) (500 mg, 550 μL, 6.16 mmol), Rose Bengal(**211**) (5.3 mg) and NaOAc (500 μL of a saturated solution, in H_2O). Solution was irradiated for 2 h to produce 5-hydroxy-1-methyl-pyrrol-2-one (**121**)(332 mg, 2.93 mmol) in a 48% yield as a yellow oil and 5-ethoxy-1-methyl-pyrrol-2-one(**243**)(110 mg, 0.78 mmol) in a 13% yield as a yellow oil, which can be separated with a gradient 20-100% ethyl acetate/hexane as the eluent system.

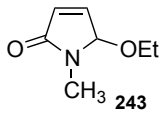
_RS_-5-hydroxy-1-methyl-pyrrol-2-one (121)



121

^{1}H NMR(400 MHz, $CDCl_3$) δ	2.91 (s, 3H), 5.28 (s, 1H), 6.07 (dd, *J* = 5.96, 0.56 Hz, 1H), 6.93 (dd, *J* = 5.96, 1.56 Hz, 1H).
^{13}C NMR(100 MHz, $CDCl_3$) δ	25.8, 85.0, 128.3, 145.7, 169.8.

_RS_-5-ethoxy-1-methyl-pyrrol-2-one (243)



243

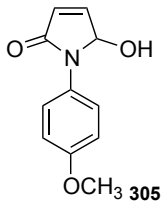
IR (thin film)	2976, 1695, 1433, 1395, 1099.
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.18 (t, *J* = 7.04 Hz, 3H), 2.91 (s, 3H), 3.31 (q, *J* = 7.04 Hz, 2H), 5.29 (s, 1H), 6.22 (d, *J* = 6.04, 1H), 6.88 (dd, *J* = 6.04, 1.52 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ	15.2, 26.1, 58.9, 89.3, 130.1, 143.6, 169.5.
MS (+EI) *m/z*	141 (M+, 10), 113 (27), 96 (100).
HRMS (+EI) *m/z*	for $C_7H_{11}NO_2$ calc. 141.07898, found 141.07939.

***RS*-5-hydroxy-1-(p-methoxyphenyl)-pyrrol-2-one (305) + *RS*-5-ethoxy-1-(p-methoxyphenyl)-pyrrol-2-one (306)**

Following the general procedure; using *N*-(*p*-methoxylphenyl)pyrrole (**173**) (182.2 mg, 1.05 mmol) and Rose Bengal (**211**) (6.2 mg). The solution was irradiated for 0.5 h to produce 5-hydroxy-1-(*p*-methoxylphenyl)-pyrrol-2-one (**305**)(46.1 mg, 0.22 mmol) in a 21% yield as a yellow oil and 5-ethoxy-1-(*p*-methoxylphenyl)-pyrrol-2-one (**306**)(22.0 mg, 0.09 mmol) in a 9% yield as a yellow oil which can be separated with a gradient 10-100% ethyl acetate/hexane as the eluent system.

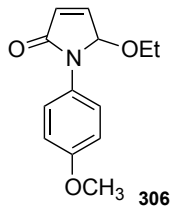
***RS*-5-hydroxy-1-(p-methoxyphenyl)-pyrrol-2-one (305)**



305

IR (thin film)	3349, 2880, 2833, 1681, 1513.
^{1}H NMR (400 MHz, $CDCl_3$) δ	3.80 (s, 3H), 5.87 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.20 (dd, *J* = 6.0, 0.8 Hz, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 7.00 (dd, *J* = 6.0, 1.6 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	55.6, 84.7, 114.5, 123.9, 129.1, 129.6, 144.8, 157.4, 168.5.
MS (+EI) *m/z*	205 (M+, 100), 188 (23), 123(93), 108 (82).
HRMS (+EI) *m/z*	for $C_{11}H_{11}NO_3$ calc. 205.07389, found 205.07464.

***RS*-5-ethoxy-1-(p-methoxyphenyl)-pyrrol-2-one (306)**



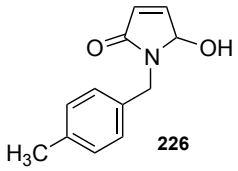
306

IR (thin film)	2976, 2916, 1695, 1514, 1392, 1104.
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.10 (t, *J* = 6.8 Hz, 3H), 3.30-3.42 (m, 2H), 3.81 (s, 3H), 5.91 (s, 1H), 6.33 (dd, *J* = 6.0, 0.8 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.98 (dd, *J* = 6.0, 1.6 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	15.2, 55.5, 59.1, 89.1, 114.4, 123.5, 130.0, 130.4, 143.6, 157.2, 168.6.
MS (+EI) *m/z*	233(M+, 82), 188 (100), 123 (28).
HRMS (+EI) *m/z*	for $C_{13}H_{15}NO_3$ calc. 233.10519, found 233.10525.

***RS*-5-hydroxy-1-(*p*-methylbenzyl)-pyrrol-2-one (226) + *RS*-5-ethoxy-1-(*p*-methylbenzyl)-pyrrol-2-one (227)**

Following the general procedure; using *N*-(*p*-methylbenzyl)pyrrole (**167**) (206.3 mg, 1.2 mmol), Rose Bengal (**211**) (4.1 mg) and NaOAc (400 μL of a saturated solution, in H_2O). The solution was irradiated for 1 h to produce 5-hydroxy-1-(*p*-methylbenzyl)-pyrrol-2-one (**226**)(131.9 mg, 0.65 mmol)in a 54% yield as a off white solid and 5-ethoxy-1-(*p*-methylbenzyl)-pyrrol-2-one (**227**)(65.7 mg, 0.28 mmol) in a 24% yield as a yellow oil which can be separated with a gradient 20-100% ethyl acetate/hexane as the eluent system.

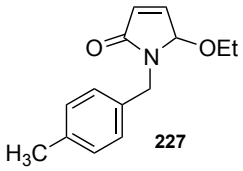
_RS_-5-hydroxy-1-(_p_-methylbenzyl)-pyrrol-2-one (226)



226

mp	98-100 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ	2.32 (s, 3H), 4.20 (d, *J* = 14.8 Hz, 1H), 4.88 (d, *J* = 14.8 Hz, 1H), 5.25 (s, 1H), 6.13 (dd, *J* = 6.0, 0.8 Hz, 1H), 6.91 (dd, *J* = 6.0, 1.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	21.1, 42.5, 82.7, 128.4, 128.6, 129.5, 134.1, 137.4, 145.8.
MS (+EI) *m/z*	203 (M+, 27), 120 (100), 105 (62).
HRMS (+EI) *m/z*	for $C_{12}H_{13}NO_2$ calc. 203.09463, found 203.09431.

_RS_-5-ethoxy-1-(_p_-methylbenzyl)-pyrrol-2-one (227)



227

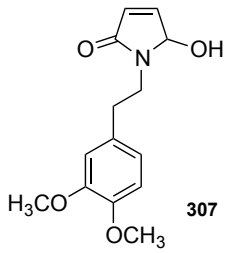
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.35 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 3.28 (q, *J* = 6.8, 2H), 4.08 (d, *J* = 14.8 Hz, 1H), 4.90 (d, *J* = 14.8 Hz, 1H), 5.28 (s, 1H), 6.24 (dd, *J* = 6.0, 0.8 Hz, 1H), 6.87 (dd, *J* = 6.0, 1.6 Hz, 1H), 7.11 (d, *J* = 8.0, 2H), 7.18 (d, *J* = 8.0 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	15.3, 21.2, 42.9, 59.3, 87.3, 128.5, 129.4, 129.9, 134.2, 137.5, 144.1, 169.4.
MS (+EI) *m/z*	231 (M+, 34), 201 (25), 120 (100).

HRMS (+EI) *m/z* for $C_{14}H_{17}NO_2$ calc. 231.12593, found 231.12685.

_RS_-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxy-pyrrol-2-one (307) + _RS_-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-ethoxy-pyrrol-2-one (308)

Following the general procedure; using *N*-[2-(3,4-dimethoxyphenyl)ethyl]-pyrrole (**175**) (292 mg, 1.26 mmol), Rose Bengal (**211**) (6 mg) and NaOAc (300 μL of a saturated solution, in H_2O). The solution was irradiated for 2 h to produce 5-hydroxy-1-[2-(3,4-dimethoxyphenyl)ethyl]-pyrrol-2-one (**307**) (113 mg, 0.42 mmol) in a 34% yield as a yellow oil and 5-ethoxy-1-[2-(3,4-dimethoxyphenyl)ethyl]-pyrrol-2-one (**308**) (73 mg, 0.25 mmol) in a 20% yield as a yellow oil, which can be separated with a gradient 70-100% ethyl acetate/hexane as the eluent system.

_RS_-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxy-pyrrol-2-one (307)



307

IR (thin film) 3360, 2936, 1682, 1511, 1263, 1235.

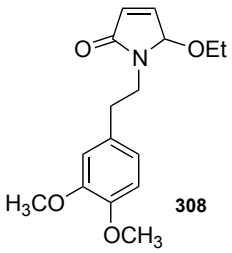
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, *J* = 7.3 Hz, 2H), 3.51 (dt, *J* = 13.9, 7.4Hz, 1H), 3.73-3.80 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 5.11 (s, 1H), 6.12 (dd, *J* = 5.9, 0.7 Hz, 1H), 6.72-6.80 (m, 3H), 6.85 (dd, *J* = 5.9, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 40.9, 55.91, 55.93, 83.8, 111.3, 112.0, 120.7, 128.8, 131.3, 145.4, 147.7, 149.0, 169.3.

MS (+EI) *m/z* 263(M+, 10), 164 (100), 151 (53).

HRMS (+EI) *m/z* for $C_{14}H_{17}NO_4$ calc. 263.11576, found 263.11621.

_RS_-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-ethoxy-1,5-dihydropyrrol-2-one (308)



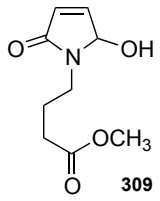
308

IR (thin film)	2928, 1695, 1516, 1262, 1235, 1141.
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.15 (t, *J* = 7.0 Hz, 3H), 2.80-2.88 (m, 2H), 3.21-3.28 (m, 2H), 3.28-3.36 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.85-3.86 (m, 1H), 5.13 (s, 1H), 6.20 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.72-6.77 (m, 3H), 6.83 (dd, *J* = 6.0, 1.6 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	15.2, 34.0, 40.8, 55.88, 55.89, 58.9, 88.1, 111.3, 111.9, 120.6, 130.0, 131.2, 143.9, 147.6, 148.9, 169.5.
MS (+EI) *m/z*	291(M+, 10), 164 (100), 151 (33), 96 (16).
HRMS (+EI) *m/z*	for $C_{16}H_{21}NO_4$ calc. 291.14706, found 291.14640.

_RS_-methyl 4-(5-hydroxy-2-oxo-pyrrol-1-yl)butyrate (309) + _RS_-methyl 4-(5-ethoxy-2-oxo-pyrrol-1-yl)butyrate (310)

Following the general procedure; using methyl 4-(pyrrol-1-yl)butyrate (**241**) (198 mg, 1.2 mmol), Rose Bengal (**211**) (4.9 mg) and NaOAc (200 μL of a saturated solution, in H_2O). The solution was irradiated for 1 h to produce methyl 4-(5-hydroxy-2-oxo-pyrrol-1-yl)butyrate (**309**)(62.1 mg, 0.2 mmol) in a 34% yield as a yellow oil and methyl 4-(5-ethoxy-2-oxo-pyrrol-1-yl)butyrate (**310**)(80.0 mg, 0.4 mmol) in a 23% yield as a yellow oil, which can be separated with a gradient 10-100% ethyl acetate/hexane as the eluent system.

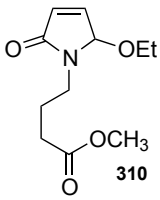
_RS_-methyl 4-(5-hydroxy-2-oxo-pyrrol-1-yl)butyrate (309)



309

IR (thin film)	3320, 2955, 1738, 1674, 1436.
^{1}H NMR (400 MHz, $CDCl_3$) δ	2.56-2.77 (m, 4H), 3.54-3.58 (m, 1H), 3.66-3.70 (m, 1H), 3.67 (s, 3H), 5.45 (s, 1H), 6.10 (dd, J = 6.0, 0.6 Hz, 1H), 6.93 (dd, J = 6.0, 1.6 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	33.3, 35.2, 52.0, 83.9, 128.2, 145.9, 161.2, 169.8, 173.5.
MS (+EI) *m/z*	185 (M-CH_3, 4), 153 (68), 110 (95), 55 (100).
HRMS (+EI) *m/z*	(M-CH_3) for $C_8H_{11}NO_4$ calc. 185.06881, found 185.06901.

_RS_-methyl 4-(5-ethoxy-2-oxo-pyrrol-1-yl)butyrate (310)

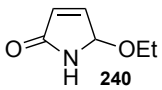


310

IR	2976, 1734, 1700, 1418, 1176.
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.18 (t, *J* = 7.0 Hz, 3H), 1.89-1.93 (m, 2H), 2.35 (t, *J* = 7.5, 2H), 3.18-3.25 (m, 1H), 3.33 (q, *J* = 7.0 Hz, 2H), 3.54-3.61 (m, 1H), 3.66 (s, 3H), 5.42 (s, 1H), 6.21 (dd, *J* = 6.0, 0.8 Hz, 1H), 6.90 (dd, *J* = 6.0, 1.6 Hz 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	15.2, 23.7, 31.4, 38.7, 51.6, 59.2, 87.8, 129.9, 143.9, 169.6, 173.4.

MS (+EI) *m/z*	227 (M+, 2), 112 (100).
HRMS (+EI) *m/z*	for $C_{11}H_{17}NO_4$ calc. 227.11576, found 227.11525.

_RS_-5-ethoxy-pyrrol-2-one



240

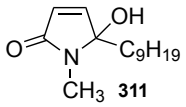
Following the general procedure; using pyrrole (**81**) (108 mg, 1.6 mmol), Rose Bengal (**211**) (3 mg) and NaOAc (100 μL of a saturated solution, in H_2O). The solution was irradiated for 1 h to produce 5-ethoxy-pyrrol-2-one (**240**) (98.2 mg, 0.77 mmol) in a 48% yield that was isolated with 100% ethyl acetate.

IR (thin film)	3245, 2979, 2883, 1684, 1374, 1107.
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.19 (t, *J* = 7.0, 3H), 3.48-3.59 (m, 2H), 5.49 (s, 1H), 6.14 (d, *J* = 5.8, 1H), 6.93 (dd, *J* = 5.8, 1.4 Hz, 1H), 7.54 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	15.2, 62.1, 85.8, 129.1, 146.4, 173.1.
MS (+EI) *m/z*	127 (M+, 4), 112 (8), 99 (35), 82 (100).
HR/MS (+EI) *m/z*	for $C_6H_9INO_2$ calc. 127.06333, found 127.06344.

_RS_-5-hydroxy-1-methyl-5-nonyl-pyrrol-2-one (311) + _RS_-5-ethoxy-1-methyl-5-nonyl-pyrrol-2-one (312)

Following the general procedure; using *N*-methyl-2-nonylpyrrole (**190**) (177 mg, 0.8 mmol), Rose Bengal (**211**) (7 mg) and NaOAc (200 μL of a saturated solution, in H_2O). The solution was irradiated for 1 h to produce 5-hydroxy-1-methyl-5-nonyl-pyrrol-2-one (**311**) (71.7 mg, 0.29 mmol) in a 35% yield as a yellow oil and 5-ethoxy-1-methyl-5-nonyl-pyrrol-2-one (**312**) (50.9 mg, 0.19 mmol) in a 22% yield as a yellow oil which can be separated with a gradient 30-60% ethyl acetate/hexane as the eluent system.

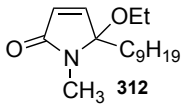
_RS_-5-hydroxy-1-methyl-5-nonyl-pyrrol-2-one (311)



311

IR (thin film)	3319, 2925, 2854, 1674, 1466.
^{1}H NMR (400 MHz, $CDCl_3$) δ	0.86 (t, *J* = 7.0 Hz, 3H), 0.95-1.04 (m, 1H), 1.10-1.16 (m, 1H), 1.20-1.30 (m, 10H), 1.55-1.62 (m, 1H), 1.73 (ddd, *J* = 13.9, 11.9, 5.0 Hz, 1H), 1.87 (ddd, *J* = 13.9, 11.9, 4.8 Hz, 1H), 2.11-2.15 (m, 1H), 2.76 (s, 3H), 5.98 (d, *J* = 5.9 Hz, 1H), 6.88 (d, *J* = 5.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	14.0, 22.6, 23.0, 23.4, 29.2, 29.3, 29.4, 29.5, 31.7, 34.6, 92.0, 126.6, 149.3, 169.4.
MS (+EI) *m/z*	239 (M+, 1), 112 (100).
HRMS (+EI) *m/z*	for $C_{14}H_{25}NO_2$, calc. 239.18853, found 239.18912.

_RS_-5-ethoxy-1-methyl-5-nonyl-pyrrol-2-one (312)

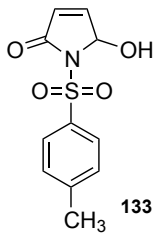


312

IR (thin film)	2925, 2855, 1699, 1390, 1080.
^{1}H NMR (400 MHz, $CDCl_3$) δ	0.84 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.0, 3H), 1.18-1.28 (m, 14H), 1.70 (ddd, *J* = 13.9, 11.9, 5.0 Hz, 1H), 1.84 (ddd, J = 13.8, 12.0, 4.8 Hz, 1H), 2.72 (s, 3H), 3.02-3.17 (m, 2H), 6.17 (d, *J* = 6.0 Hz, 1H), 6.74 (d, *J* = 6.0 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	14.0, 15.2, 22.6, 23.18, 23.19, 29.2, 29.3, 29.4, 29.5, 31.8, 35.0, 58.2, 95.6, 129.0, 147.3, 169.3.

MS (+EI) *m/z*	268 (M+H, 32), 222 (18).
HRMS (+EI) *m/z*	for $C_{16}H_{30}NO_2$, calc. 268.2277, found 268.2268.

_RS_-5-hydroxy-1-(*p*-tolylsulfonyl)-pyrrol-2-one (133)

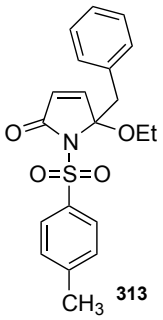


133

Following the general procedure; using *N*-tosylpyrrole (**108**) (103 mg, 0.46 mmol), Rose Bengal (**211**) (2.5 mg) and NaOAc (200 μL of a saturated solution, in H_2O). The solution was irradiated for 2 h to produce 5-hydroxy-1-(*p*-tolylsulfonyl)-pyrrol-2-one (**133**)(34.9 mg, 0.14 mmol) in a 30% yield that was isolated with a gradient 10-100% ethyl acetate/hexane as the eluent system. Spectra collected matched that reported within the literature.[78]

^{1}H NMR (300 MHz, $CDCl_3$) δ	2.44 (s, 3H), 6.06 (d, *J* = 6.0 Hz, 1H), 6.22 (s, 1H), 7.07 (dd, *J* = 6.0, 1.8 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	21.8, 83.4, 127.8, 128.2, 129.9, 135.4, 145.5, 147.6, 166.3.

_RS_-5-benzyl-5-ethoxy-1-(*p*-tolylsulfonyl)-pyrrol-2-one (313)



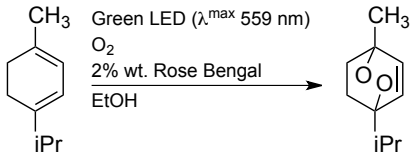
313

Following the general procedure; using 2-benzyl-*N*-tosylpyrrole (**242**) (259 mg, 0.8 mmol), Rose Bengal (**211**) (5 mg) and NaOAc (200 μL of a saturated solution, in

H_2O). The solution was irradiated for 2 h to produce 5-benzyl-5-ethoxy-1-(*p*-tolylsulfonyl)-pyrrol-2-one (**313**) (101.3 mg, 0.27 mmol) in a 33% yield that was isolated with 25% ethyl acetate/hexane as the eluent system.

^{1}H NMR (400 MHz, $CDCl_3$) δ	1.15 (t, *J* =6.8 Hz, 3H), 2.41 (s, 3H), 3.09-3.20 (m, 2H), 3.22 (d, *J* = 13.6 Hz, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 5.94 (d, *J* =6.2 Hz, 1H), 6.66 (d, *J* = 6.2 Hz, 1H), 7.13-7.28 (m, 5H), 7.31 (d, *J* =8.0 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	14.9, 21.7, 44.7, 60.4, 100.3, 126.3, 127.2, 128.3, 128.5, 129.5, 130.7, 135.0, 136.6, 145.1, 151.2, 167.0.
MS (+EI) *m/z*	391 (M+Na, 17), 326 (45).
HRMS (+EI) *m/z*	for $C_{20}H_{21}NNaO_4S$, calc. 394.1084, found 394.1080.

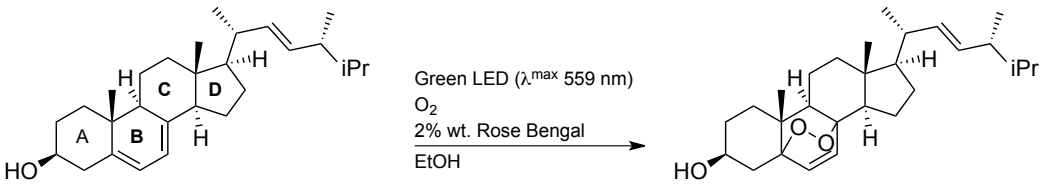
The photo-oxidation of α-terpinene



Into the red LED photo-reactor was added methylene blue (**212**) (0.9 mg) and α-terpinene (**223**) (103 mg, 0.75 mmol) followed by EtOH (100 mL). O_2 was bubbled through the solution while the light was on for 1 h before the solution was evaporated to yield ascaridole (**224**) (127 mg, 0.75 mmol). The ^{1}H NMR spectrum collected matched that within the literature.[107]

^{1}H NMR (400 MHz, $CDCl_3$) δ	0.99 (d, *J* = 6.9 Hz, 6H), 1.37 (s, 3H), 1.48-1.55 (m, 2H), 1.92 (sept, *J* = 6.9 Hz, 1H), 1.98-2.07 (m, 2H), 6.40 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H).

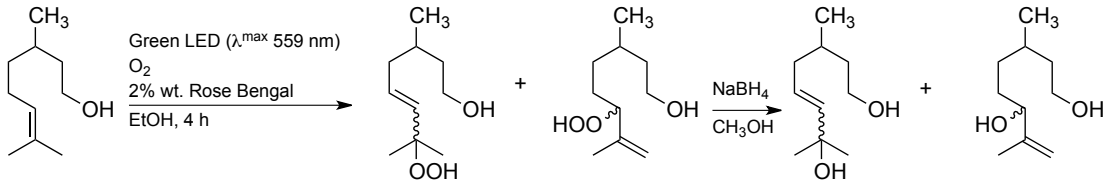
The photo-oxidation of ergosterol



Into the green LED photo-reactor was added Rose Bengal (**211**) (7.0 mg) and ergosterol (**244**) (100 mg, 0.25 mmol) followed by EtOH (75 mL). O_2 was bubbled through the solution for 1 h with the light on. After this time the solution was evaporated, and purified on the automated flash chromatography system with a gradient elution of 10-100% ethyl acetate/hexanes to isolate **246** (86.4 mg, 0.20 mmol) in a 79% yield. The ^{1}H NMR spectrum collected matched that within the literature.[112]

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, *J* = 5.3 Hz, 6H), 0.83 (s, 3H), 0.87 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.18-2.12 (m, 21H), 3.94 (sept, *J* = 5.3 Hz, 1H), 5.10-5.24 (m, 2H), 6.22 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H).

The photo-oxidation of citronellol

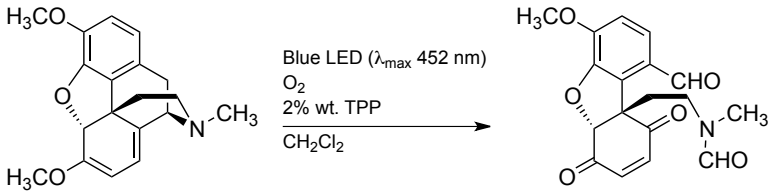


Into the green LED photo-reactor was added Rose Bengal (**211**) (5.7 mg) and citronellol (**220**) (200 mg, 1.28 mmol) followed by EtOH (100 mL). O_2 was bubbled through the solution for 4 h with the light on. After this time the solution was evaporated, redissolved and purified on a short plug of silica gel with 100% ethyl acetate to isolate the mixture of **222** and **221** (218 mg, 1.16 mmol) in a 91% yield and 3:4 ratio. While a common synthetic intermediate, there was no ^{1}H NMR literature data for the peroxides. Thus, the peroxides were treated with $NaBH_4$ (109 mg, 2.89 mmol) in CH_3OH (10 mL) for 1 h to produce the analogous alcohols **315**

and **314**. The ^{1}H NMR spectrum collected for the alcohols matched that within the literature.[107]

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89-0.95 (m, *both isomers*), 1.30 (s, 6H, *sec*), 1.32-1.68 (m, *both isomers*), 1.72 (s, 3H, *tert*), 1.88-2.06 (m, *both isomers*), 3.58-3.70 (m, 2H, *tert*), 4.98-4.02 (m, 1H, *sec*), 4.76-4.83 (m, 1H, *sec*), 4.87-4.94 (m, 1H, *sec*), 5.52-5.61 (m, 2H, *tert*).

The photolysis of thebaine

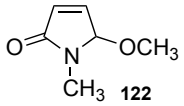


Into the blue LED photo-reactor was added TPP (**213**) (5.7 mg) and thebaine (**247**) (200 mg, 0.64 mmol) followed by CH_2Cl_2 (100 mL). O_2 was bubbled through the solution for 1 h with the light on. After this time the solution was evaporated, redissolved and purified on a short plug of silica gel with 100% ethyl acetate to isolate formamide **248** (202 mg, 0.59 mmol) in a 91% yield. The ^{1}H NMR spectrum collected matched that within the literature.[114] The ^{1}H NMR spectrum displayed as a mixture of rotomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24-2.31 (*major*, m, 1H), 2.35-2.43 (*minor*, m, 1H), 2.50-2.57 (*minor*, m, 1H), 2.59-2.67 (*major*, m, 1H), 2.77 (*minor*, s, 3H), 2.91 (*major*, s, 3H), 3.03-3.10 (*major*, m, 1H), 3.13-3.29 (*minor*, m, 2H), 3.57-3.65 (*major*, m, 1H), 3.91 (*major*, s, 3H), 3.94 (*minor*, s, 3H), 5.00 (*minor*, s, 1H), 5.31 (*major*, s, 1H), 6.83-6.98 (*major* + *minor*, m, 3H), 7.55 (*major* + *minor*, d, J = 8.8 Hz, 1H), 7.84 (*major*, s, 1H), 7.87 (*minor*, s, 1H), 10.03 (*minor*, s, 1H), 10.18 (*major*, s, 1H).

5.4 Experimental for Chapter 4

_RS_-5-methoxy-1-methyl-pyrrol-2-one (122)

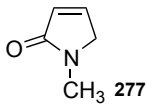


122

To a solution of **116a** (28.3 mg, 0.082 mmol) in CH_3OH (2 ml) at 0 °C, was added TMSCl (32 μL, 0.25mmol). The reaction mixture was allowed to stir for 3 h before removing the solvent under reduced pressure. The residue was taken up in ethyl acetate (10 mL) and washed with a 1:1 mixture of saturated $NaHCO_3$ and H_2O (2 × 10 mL) followed by a solution of saturated NaCl (10 mL). The organic layer was dried on Na_2SO_4, filtered and evaporated under reduced pressure to yield **122** (8.3 mg, 0.065 mmol) in a 79% yield as a brown oil. No further purification was required. Spectra consistent with literature values.[65]

^{1}H NMR (300 MHz, $CDCl_3$) δ	2.92 (s, 3H), 3.10 (s, 3H), 5.31 (s, 1H), 6.27 (d, *J* = 5.9 Hz, 1H), 6.84-6.89 (m, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	26.3, 50.5, 89.8, 131.0, 143.4, 170.0.

1-Methyl-1,5-dihydropyrrol-2-one (277)

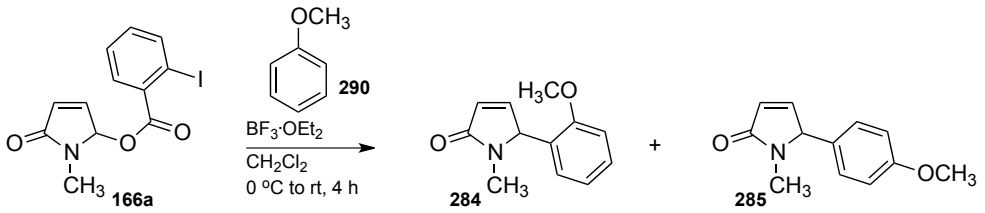


277

To a solution of **166a** (42.8 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added triethylsilane (42 μL, 30.5 mg, 0.26 mmol) followed by BF_3•OEt_2 (35 μL, 40.2 mg, 0.28 mmol). The mixture was allowed to warm to room temperature and left to stir for 20 h before quenching with saturated K_2CO_3 (5 ml). The organic layer was removed before extracting the aqueous layer with $CHCl_2$ (3 x 5 mL). The combined organic fractions were dried on Na_2SO_4 and filtered before removing solvent under reduced pressure to yield **277** (9.4 mg, 0.09 mmol) in a 78% yield as brown oil. No further purification was required. Spectra consistent with literature values.[140]

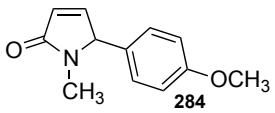
^{1}H NMR (300 MHz, $CDCl_3$) δ	3.04 (s, 3H), 3.95-3.99 (m, 2H), 6.18 (dt, *J* = 6.0, 1.9 Hz, 1H), 7.04 (dt, *J* = 6.0, 1.7 Hz).
^{13}C NMR (75 MHz, $CDCl_3$) δ	29.2, 54.9, 128.6, 142.4, 173.3.

***RS*-5-(*p*-methoxyphenyl)-1-methyl-1,5-dihydropyrrol-2-one (284) + *RS*-5-(*o*-methoxyphenyl)-1-methyl-1,5-dihydropyrrol-2-one (285)**



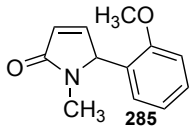
To an oven dry flask was added 2-pyrrolinone **166a** (63.1 mg, 0.18 mmol) followed by methoxybenzene (**290**) (30 μL, 28.8 mg, 0.27 mmol) and dry CH_2Cl_2 (1.8 mL) at 0 °C. The reaction was stirred for 18 h after which time the reaction flask had reached room temperature. After this time the reaction was quenched with a saturated solution of K_2CO_3 (5 mL) before being extracted with CH_2Cl_2 (3 × 5 mL). The organic fractions were dried on $MgSO_4$ before the solvent was removed under reduced pressure to yield the crude oil. The mixture was purified by flash column chromatography on silica gel to isolate 5-(*p*-methoxyphenyl)-1-methyl-1,5-dihydropyrrol-2-one (**284**) (25.8 mg, 0.12 mmol) in a 69% yield and 5-(*o*-methoxyphenyl)-1-methyl-1,5-dihydropyrrol-2-one (**285**) (10.9 mg, 0.05 mmol) in a 29% yield.

***RS*-5-(*p*-methoxyphenyl)-1-methyl-1,5-dihydropyrrol-2-one (284)**



^{1}H NMR (300 MHz, $CDCl_3$) δ	2.79 (s, 3H), 3.81 (s, 3H), 4.92 (s, 1H), 6.21 (dd, *J* = 5.7, 1.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 5.7, 1.8 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	27.0, 55.4, 68.3, 114.6, 126.4, 126.6, 128.5, 147.8, 160.0, 171.5.
MS (+EI) *m/z*	203 (M+, 35), 87 (77).
HRMS (+EI) *m/z*	for $C_{12}H_{13}NNO_2$, calc. 203.09463, found 203.09434.

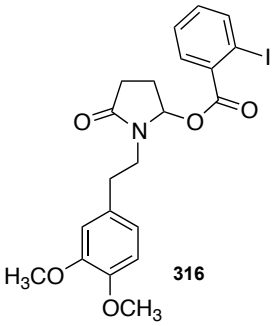
***RS*-5-(*o*-methoxyphenyl)-1-methyl-1,5-dihydropyrrol-2-one (285)**



285

^{1}H NMR (300 MHz, $CDCl_3$) δ	2.86 (s, 3H), 3.89 (s, 3H), 5.56 (s, 1H), 6.18 (dd, *J* = 5.7, 1.8 Hz, 1H), 6.85-6.69 (m, 2H), 7.04 (d, *J* =5.7, 1.8 Hz, 1H), 7.30 (dt, *J* = 7.5, 2.1 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ	27.4, 55.6, 62.4, 110.9, 121.2, 122.6, 126.3, 126.7, 129.5, 147.8, 157.4, 172.2.
MS (+EI) *m/z*	203 (M+, 35), 148 (30), 87 (72).
HRMS (+EI) *m/z*	for $C_{12}H_{13}NNO_2$, calc. 203.09463, found 203.09511.

***RS*-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-oxo-2-pyrrolidinyl-*o*-iodobenzoate (316)**



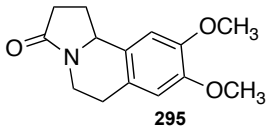
316

1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-oxo-pyrrol-2-yl *o*-iodobenzoate (**176**) (108.7 mg, 0.22 mmol) was dissolved in EtOH (10 mL) before addition of Pd/C (~13 % wt/wt, 14.5 mg) and reacted with H_2 (40 psi) in a Parr Shaker Hydrogenation apparatus for 6 h at room temperature. The resulting suspension was filtered through a short plug of Celite® before solvent was removed under reduced pressure to yield **316** (81.9 mg, 0.16 mmol) in a 75% yield as a brown oil. The compound was deemed pure enough to use in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.87-1.99 (m, 1H), 1.99-2.11 (m, 1H), 2.25-2.38 (m, 1H), 2.46-2.69 (m, 1H), 2.76-2.89 (m,

2H), 3.323.44 (m, 2H), 3.85 (s, 3H), 3.86 (s 3H), 4.70 (d, *J* = 4.8 Hz), 6.71-6.80 (m, 3H), 7.49-7.65 (m, 2H), 7.89-8.06 (m, 2H).

_RS_-8,9-dimethoxy-1,5,6,10*b*-tetrahydro-2H-pyrrolo[2,1-*a*]isoquinolin-3-one (295)

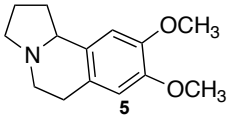


295

To a solution of **316** (81.9 mg, 0.16 mmol) in $CHCl_2$ (1.5 mL) at 0^oC was added BF_3•OEt_2 (62 µL, 71.3 mg, 0.5 mmol). The mixture was allowed to warm to room temperature and left to stir for 1 h before quenching with saturated K_2CO_3 (5 ml). The organic layer was removed before extracting the aqueous layer with $CHCl_2$ (3 x 5 mL). The combined organic fractions were dried on Na_2SO_4 and filtered before removing solvent under reduced pressure. The crude mixture was purified by flash chromatography with 100% ethyl acetate as the eluent to yield **295** (34 mg, 0.14 mmol) in an 83% yield as yellow oil. No further purification was required. The ^1H NMR spectrum was consistent with literature values.[130]

^1H NMR (300 MHz, $CDCl_3$) δ 1.79-1.89 (m, 1H), 2.40-2.71 (m, 4 H), 2.78-2.93 (m, 1 H), 2.99 (td, *J* = 11.7, 4.2 Hz, 1 H), 3.85 (s, 3H), 3.86 (3H), 4.26-4.33 (m, 1H), 4.71 (t, *J* = 7.8 Hz), 6.55 (s, 1H), 6.60 (s, 1H).

_RS_-Crispine A (5)



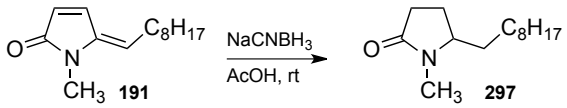
5

Following the method of Shirakawa et al., **295** (29.7 mg, 0.12 mmol) was reacted to crispine A (**5**) (22.2 mg, 0.095 mmol, 79 %). The ^1H NMR spectrum was consistent with literature values.[130]

^1H NMR(300 MHz, $CDCl_3$) δ 1.62- 1.78 (m, 1H), 1.77- 1.96 (m, 2 H), 2.25-2.36 (m, 1H), 2.53- 2.77 (m, 3H), 2.95- 3.09

(m, 2H), 3.13- 3.19 (m, 1H) 3.41 (t, *J*= 8.4 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 6.55 (s, 1H), 6.59 (s, 1H).

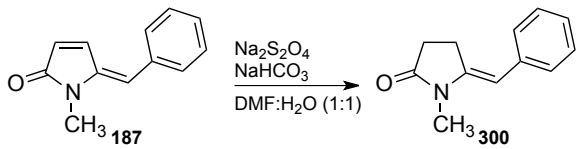
_RS_-1-methyl-5-nonyl-2-pyrrolidinone (297)



To a solution of 2-pyrrolinone **191** (216.3 mg, 0.97 mmol) in AcOH (9 mL) was added $NaCNBH_3$ (117.8 mg, 1.87 mmol) at room temperature. The reaction mixture was stirred for 5 h before it was concentrated under reduced pressure. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added to the resultant concentrate that was further extracted with CH_2Cl_2 (3 × 10 mL). The organic fractions were dried on $MgSO_4$ before the solvent was removed under reduced pressure to yield 2-pyrrolidinone **297** (212.4 mg, 0.92 mmol) in a 96% yield.

^{1}H NMR(400 MHz, $CDCl_3$) δ	0.85 (t, *J* = 6.8 Hz, 3H), 1.11-1.30 (m, 16H), 1.57-1.72 (m, 1H), 2.06-2.14 (m, 1H), 2.22-2.40 (m, 2H), 2.75 (s, 3H), 3.39-3.46 (m 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	14.1, 22.7, 24.0, 24.5, 27.7, 29.3, 29.5, 29.6, 29.7, 30.2, 31.9, 33.3, 60.0, 175.1.
MS (+EI) *m/z*	224 (M+, 3), 98 (100).
HRMS (+EI) *m/z*	for $C_{14}H_{27}NO$ calc. 225.20926, found 225.20933.

(E)-5-Phenylmethylidene-1-methyl-2-pyrrolidinone (300)



To a solution of 2-pyrrolinone **187** (55.6 mg, 0.30 mmol) dissolved in a 1:1 mixture of H_2O/DMF (2 mL) was added $Na_2S_2O_4$ (104.5 mg, 0.60 mmol) and (50.4 mg, 0.6 mmol) at room temperature. The reaction was stirred for 2 h before diluting with H_20

(10 mL) and extracting with a 1:1 mixture of ethyl acetate/hexanes. The organic fractions were collected and dried on $MgSO_4$ before the solvent was removed on reduced pressure. 2-Pyrrolidinone **300** (24.6 mg, 0.13 mmol) was isolated by flash column chromatography on silica gel as an off white solid in 44% yield.

mp	62-64 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ	2.55-2.59 (m, 2H), 2.97-3.02 (m, 2H), 3.07 (s, 3H), 5.74 (s, 1H), 7.13-7.18 (m, 1H), 7.25-7.34 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ	23.9, 26.9, 29.2, 102.8, 125.6, 127.7, 128.6, 136.8, 143.3, 175.4.
MS (+EI) *m/z*	187 (M+, 100), 158 (45), 116 (32).
HRMS (+EI) *m/z*	for $C_{12}H_{13}NO$ calc. 187.09971, found 187.09942.

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Part 2: The strain driven rearrangement of cyclopropenyl trichloroacetimidates.

Chapter 6 – Introduction

6.1 Cyclopropenes and Alkylidenecyclopropanes

Three membered carbocycles have received much attention in the contemporary literature.[1-8] This is due to unusual reactivity that leads to a large scope of potential reactions that can be performed on these small molecules, which in turn leads to them becoming versatile building blocks in organic synthesis. The large variety of reactions possible on three membered carbocycles is a result of the high ring strain energy found within the three membered rings. This strain can be partially attributed to the rings angular strain, as well as the rings torsional strain (Figure 1).

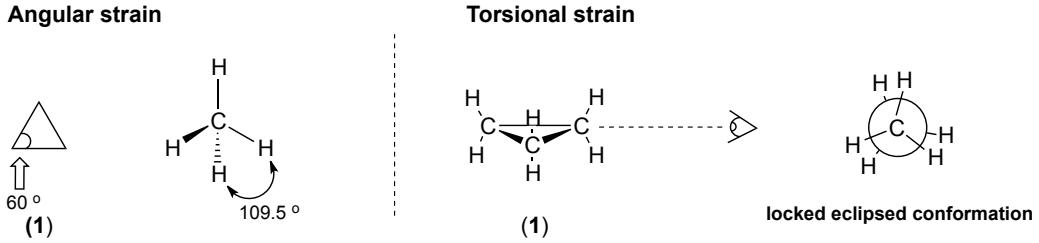


Figure 1: *Graphical representation of both the angular strain and torsional strain experienced by three membered carbocycles*

Within the family of three membered carbocycles, the cyclopropene contains the highest ring strain energy. This results from the molecule containing two sp^2 hybridised carbons atoms and a single sp^3 hybridised carbon atom adopting a 60 ° bond angle, which is highly unfavourable. It is well known that sp^3 hybridised carbon atoms adopt tetrahedral geometry resulting in an idealised bond angle of 109.5 °, while sp^2 hybridised carbon atoms have an idealised bond angle of 120 °. Of course, in comparison to the saturated cyclopropane, which contains three sp^3 hybridised carbon atoms, the ring strain energy is significantly higher in cyclopropenes (Figure 2).

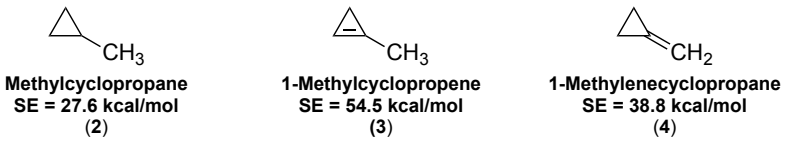
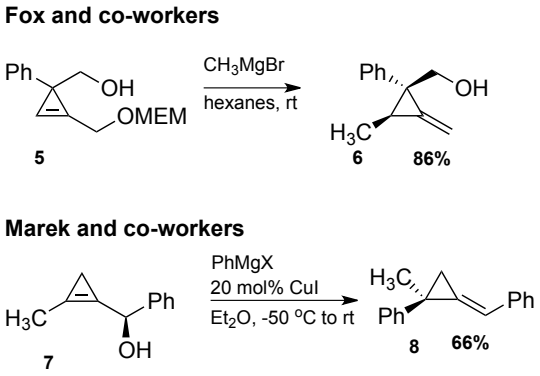


Figure 2: *Comparative structures and the associated strain energies of three membered carbocycles*

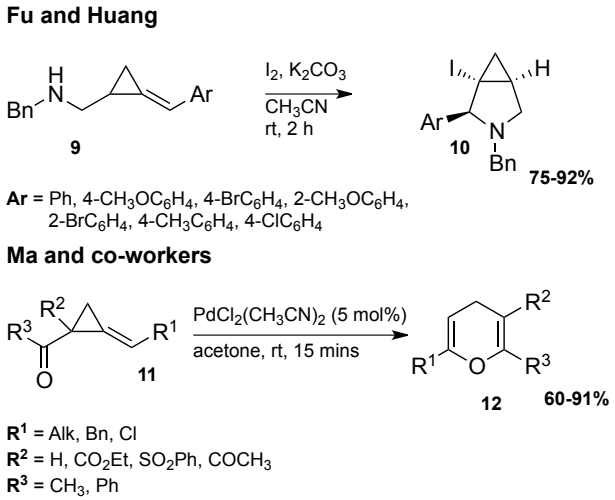
While the strain energy is partially derived from the two sp^2 hybridised carbons in the ring adopting a tight bond angle, calculations performed by Johnson and Borden suggest that the primary contributor to the increased strain energy is the removal of the strong C−H cyclopropane bonds.[9] The remaining sp^3 hybridised C−H bonds within the cyclopropene ring are now allylic, which results in much weaker bonds, thus increasing the ring strain energy.[10] Due to these factors, the resultant strain energy in 1-methylcyclopropene (**3**) is 54.5 kcal/mol, which is essentially double that found in the parent cyclopropane at 27.6 kcal/mol (Figure 2).[11] This exceptionally high strain energy found within the cyclopropene ring results in the high reactivity to alleviate the strain, and as such, cyclopropenes do not react as typical alkenes. An example of this divergence from typical alkene reactivity is the addition of Grignard reagents to the cyclopropene as demonstrated by the groups of Fox and Marek (Scheme 1).[12,13]



Scheme 1: *Examples of the addition of Grignard reagents to cyclopropenes to alleviate the high ring strain*

Energetically sitting between the strain energies of methylcyclopropane (**2**) and 1-methylcyclopropene (**3**) is 1-methylenecyclopropane (**4**) at 38.8 kcal/mol (Figure 2).[11] While the molecule still contains weak allylic C−H bonds, making its strain energy higher than cyclopropane, the reduction of energy in relation to cyclopropene is due to only a single sp^2 hybridised carbon present within the ring, lowering the angular strain. Methylene-, or alkylidenecyclopropanes are arguably more interesting than other three membered carbocycles as a building block in organic synthesis, due to the exocyclic double bonds potential for serving as a synthetic handle for further synthetic manipulation.[1,14] Similar to that of the cyclopropene, any reduction of, or addition to, the alkene will be promoted favourably due to the relief of strain. Two

excellent examples of the rapid modification of the alkylidenecyclopropane unit to complex small molecules are those reports by both Fu and Huang, and Ma and co-workers.[15,16] Fu and Huang reported the production of densely functionalised pyrrolidines form the iodocyclisation of substituted alkylidenecyclopropanes, without the loss of the cyclopropane ring, while Ma and co-workers reported a ring-opening cycloisomerisation trough chloropalladation to produce a range of substituted pyrans (Scheme 2).

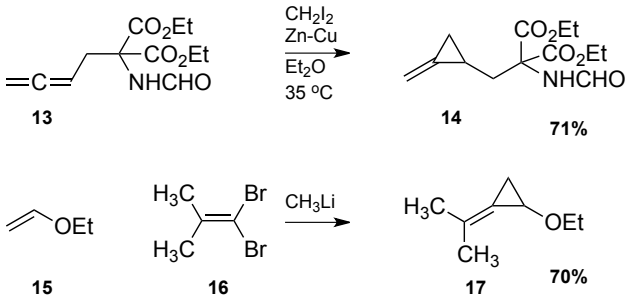


Scheme 2: *Two examples of the rapid modification to the alkylidenecyclopropane unit to generate densely functionalised molecules*

While they are synthetically useful as precursors to synthetically diverse molecules, the synthesis of alkylidenecyclopropanes remains much less developed than that of cyclopropenes. As such, a detailed discussion on the production of molecules containing these carbocyclic cores will follow.

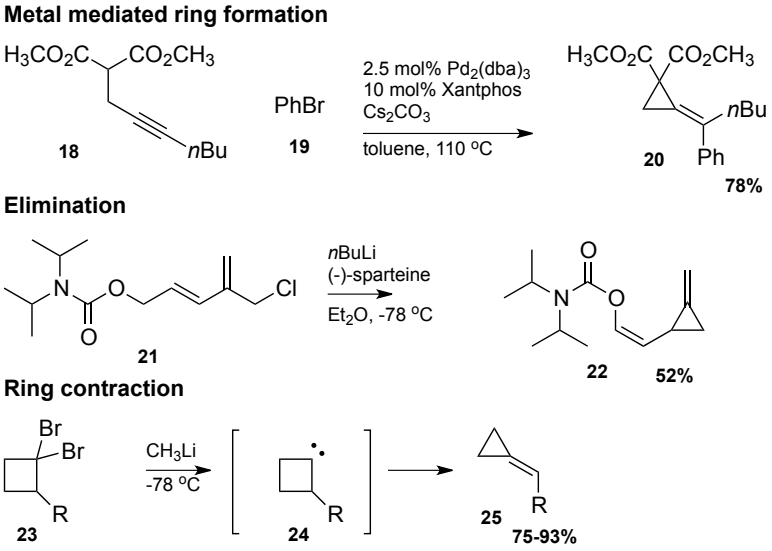
6.2 Synthesis of Alkylidenecyclopropanes

Alkylidenecyclopropanes can be synthesised from acyclic starting materials by a number of different methods, and as with other three membered carbocycles a common synthesis employs the Simmons−Smith reaction.[17,18] This transformation involves the addition of an organozinc carbenoid across an allene or an alkylidene carbene to an alkene to produce densely functionalised alkylidenecyclopropanes (Scheme 3).[19]



Scheme 3: *The addition of carbenoids across alkenes to produce densely functionalised alkylidenecyclopropanes*

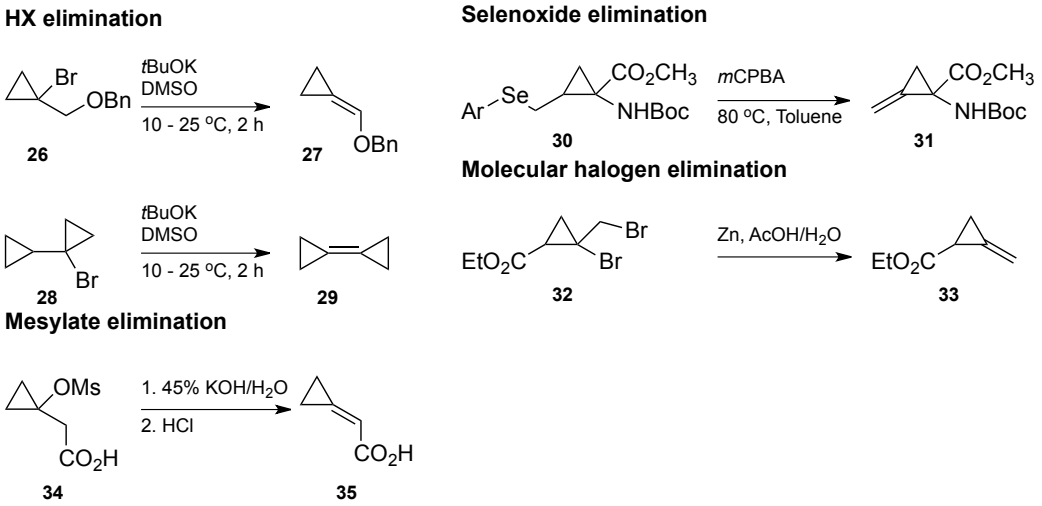
Other common methods for synthesising alkylidenecyclopropanes from acyclic starting materials involve intramolecular metal mediated ring formations from substituted alkynes,[20] or elimination followed by intramolecular capture of the resultant carbocation (Scheme 4).[21] Also while not acyclic, ring contraction reactions of cyclobutanes can also yield alkylidenecyclopropanes.[22] However, for the purposes of this discussion, a focus on those syntheses of alkylidenecyclopropanes formed from pre-existing cyclopropanes and cyclopropenes will be detailed.



Scheme 4: *Selected examples of Alkylidenecyclopropanes syntheses*

Commonly, methylene- or alkylidenecyclopropanes are produced from an elimination reaction performed on a functionalised cyclopropane.[23,24] This base assisted elimination has been shown on a range of different cyclopropanes containing different functionalities, with several different leaving groups participating in the reaction, the most common of which is the elimination of halo acids (i.e. HCl). This

has been exemplified by the research of de Meijere and co-workers who have used the elimination of HBr and HCl exclusively in their construction of alkylidenecyclopropanes (Scheme 5). The exocyclic alkene can also be produced from the elimination of other leaving groups such as selenoxides,[25-27] tosylates,[28,29] mesylates,[30,31] and dihalogens.[32]



Scheme 5: *Various examples of elimination reactions used in the production of alkylidenecyclopropanes*

Nucleophilic displacements and rearrangements of substituted cyclopropenes and allylic cyclopropanes have also been shown to be highly effective in the synthesis of alkylidenecyclopropanes. The production of alkylidenecyclopropanes from allylic cyclopropanes commonly involves a palladium catalyst to initiate a shift of the double bond to the exocyclic position of the molecule, going through a π–allylpalladium complex intermediate. While a range of leaving groups has been used to help facilitate these reactions, tosylates are most commonly employed. The common π–allylpalladium complex intermediate **38** can be formed by oxidative addition of Pd-(0) to the initial cyclopropane, regardless of where the leaving group is in relation to the cyclopropane (Figure 3). However the product is governed by the type of nucleophile added, which is a common feature in these types of allylic-palladium rearrangements.[1,23] On treatment of the complex with a soft nucleophile, an alkylidenecyclopropane will be formed; yet on treatment with a hard nucleophile, nucleophilic substitution will occur on the face of the cyclopropane ring, forcing the double bond back into an allylic position.

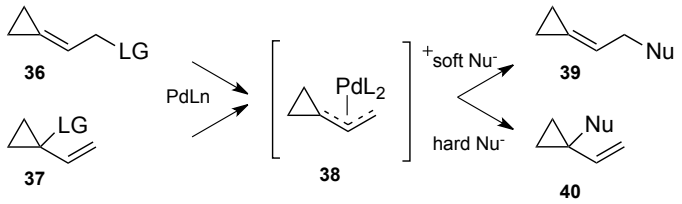
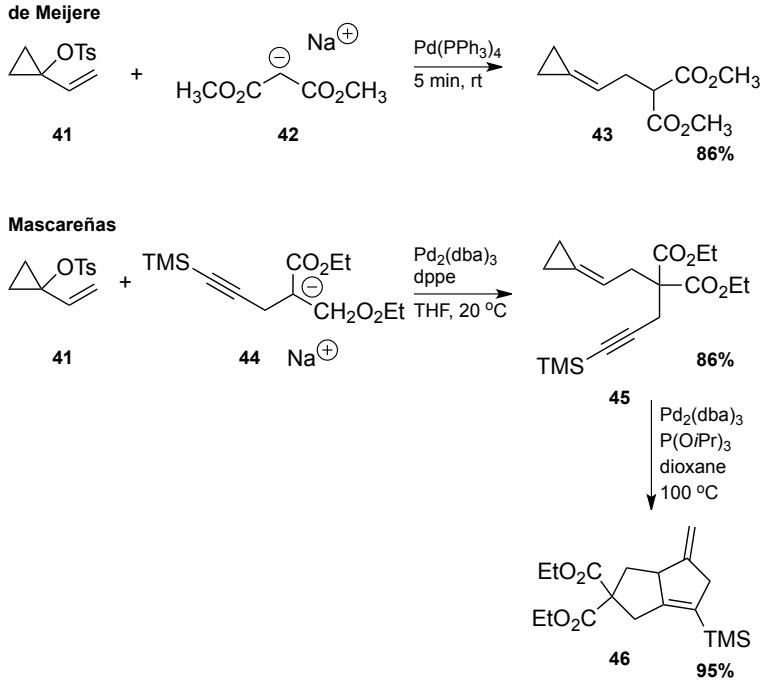


Figure 3: *The transition metal mediated allylic rearrangement of cyclopropanes.*

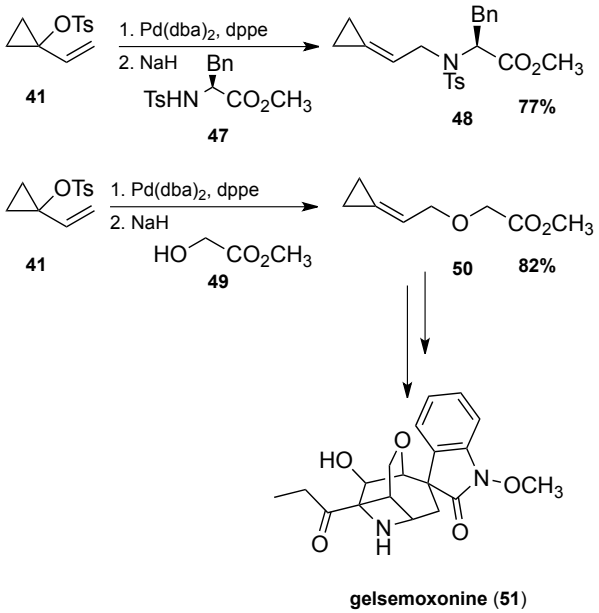
The use of nucleophilic displacement of an allylic alkene on cyclopropanes has been used with carbon, oxygen and nitrogen nucleophiles to generate various functionalised alkylidenecyclopropanes. Using the sodium salt of dimethyl malonate (**42**) as the soft carbon nucleophile, de Meijere and co-workers demonstrated the palladium mediated synthesis of alkylidenecyclopropane **43** (Scheme 6).[33] This synthesis was further utilised by Mascareñas and co-workers in their study into the palladium catalysed [3+2] intramolecular cyclisation of alk-5-ynylidenecyclopropane **45**.[34]



Scheme 6: *Examples from the groups of de Meijere and Mascareñas for the palladium-mediated synthesis of alkylidenecyclopropanes from an allylic rearrangement.*

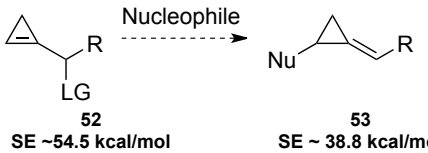
While there hasn't been an abundance of examples concerning the inclusion of heteroatom nucleophiles in the palladium allylic substitution reaction, Brandi and Salaün have shown that protected amine and alcohol containing nucleophiles could

be added to tosylates **41**(Scheme 7).[35] Furthermore, this development has been utilised by Diethelm and Carreira in their total synthesis of the *Gelsemium* alkaloid gelsemoxonine (**51**).



Scheme 7: *Brandi and Salaün example of using heteroatom nucleophiles in the palladium-mediated allylic rearrangement of cyclopropanes.*

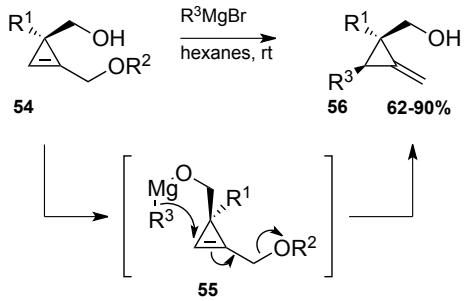
As alluded to above, examples of Tsuji type allylic substitutions to synthesise alkylidenecyclopropanes has been primarily focused upon using highly strained cyclopropenes as starting materials. As discussed, resulting from several factors, the strain energy in any given cyclopropene ring (**52**) is significantly higher than in the analogous alkylidenecyclopropane (**53**), and it is the lowering of this strain energy that promotes the conversion to alkylidenecyclopropanes (Scheme 8).



Scheme 8: *Illustrative example of the general rearrangement from a cyclopropene to an alkylidenecyclopropane.*

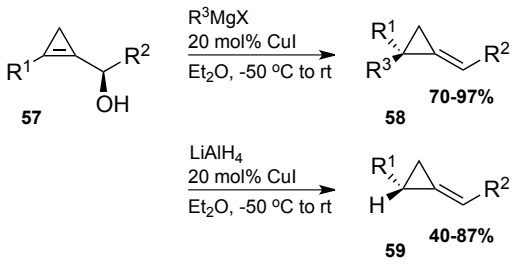
The groups of Fox and Marek have both achieved nucleophilic displacement of the internal alkene to produce alkylidenecyclopropanes. Fox and co-workers have shown that upon treatment with a range of Grignard reagents, cyclopropenes (**54**) will

produce methylenecyclopropanes (**56**) in good to excellent yields (Scheme 9).[36] Drawing evidence from previous observations,[12] Fox and co-workers explain that having a pendant alcohol at C3 aids in the facially selective attack of the nucleophile at the desired position, while the allylic -OR groups serves as a good leaving group. The selectivity is postulated to be a result of coordination of the magnesium from the Grignard reagent with the oxygen atom, guiding the nucleophile to be delivered to that face of the cyclopropene (Scheme 9).



Scheme 9: *Fox and co-workers nucleophilic displacement*

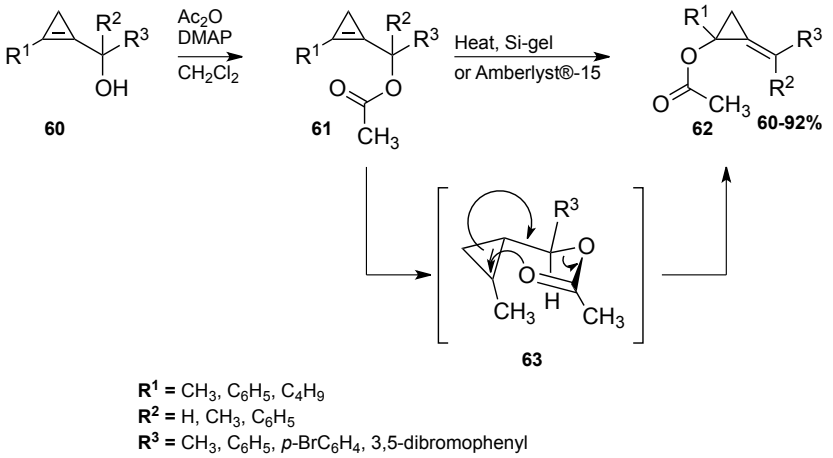
Marek and colleagues have performed similar research to that of Fox and co-workers in the synthesis of densely substituted alkylidenecyclopropanes directly from cyclopropenylcarbinols (**57**) (Scheme 10).[13,37] In the reactions performed by Marek and co-workers, organo-copper reagents are used to form a tertiary carbon centre on the cyclopropane ring, while simultaneously shifting the alkene to the exocyclic position. Similar to the observations made by Fox, the use of an allylic hydroxyl group is employed to assist in the facial selectively by coordination with the metal, however as a consequence of the reaction, the alcohol is eliminated as the alkene shifts to the exocyclic position. Marek observes that without the addition of CuI to the reaction mixture (and hence no generation of the organo-copper reagent), no reaction occurs, which matches that of Fox's observations in only having success with modified alcohols.[38] Further to the carbon nucleophiles, Marek and co-workers have also adapted the reaction conditions for the addition of a hydride, in the form of $LiAlH_4$, without reduction of the alkene functionality.[37] Again, the copper reagent is necessary in this modification, as without it the alkene is reduced. Both Marek and Fox report that these displacements are favourable due to the cyclopropenylcarbinol strain energy.



57 **58** **59**

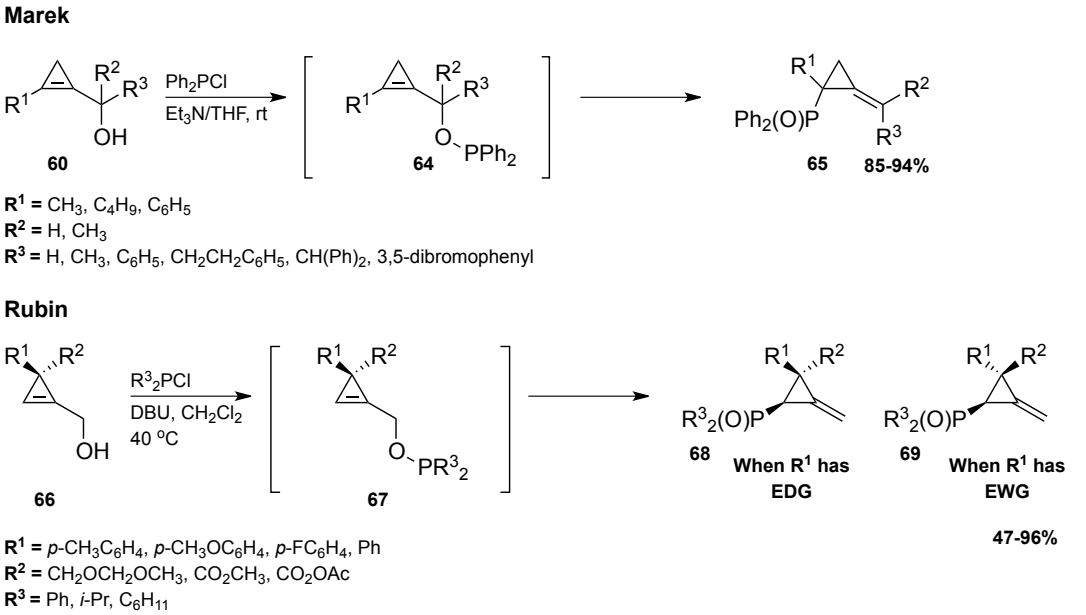
Scheme 10: *Marek and co-workers organo-copper nucleophilic displacement to produce alkylidenecyclopropanes directly from cyclopropenylcarbinols.*

Marek and co-workers have also developed an intramolecular [3,3]-sigmatropic rearrangement on cyclopropenes to give a library of alkylidenecyclopropanes featuring tertiary heteroatom substituents on the cyclopropane ring (Scheme 11).[39] They were able to produce a library of the cyclopropenyl acetates (**61**) from cyclopropenylcarbinols (**60**) *via* the intramolecular transfer of acetate. When treated under extremely mild conditions the cyclopropenyl acetates underwent an energetically favourable [3,3]-sigmatropic rearrangement, due to the strain relief of the cyclopropene. This rearrangement was shown to proceed under three separate reaction conditions: by heating to reflux in CH_2Cl_2; running through a column of silica gel; or stirring with the acidic ion-exchange resin Amberlyst®-15. This rearrangement was achieved with a range of substrates with varying degrees of functionality to give a range of alkylidenecyclopropanes (**62**) in high to excellent yields. The *E*-isomer was consistently observed to be dominant in all cases, which can be explained by the proposed chair like conformation adopted in the transition state (**63**) where R^3 occupies a pseudoequitorial position (Scheme 11).



Scheme 11: *The [3,3]-sigmatropic rearrangement of cyclopropenyl acetates to alkylidenecyclopropanes developed by Marek and co-workers*

Marek and Rubin have independently developed a [2,3]-sigmatropic rearrangement of cyclopropenylcarbinol derived molecules.[38-40] Both groups treat various cyclopropenylcarbinols (**60** & **66**) with a base and a chlorophosphine to generate a cyclopropenylalkylphosphinite (**64** & **67**), which rearranges readily to various alkylidenecyclopropylphosphine oxides (**65** and **68**, **69**) (Scheme 12). Whereas Marek and co-workers demonstrated this rearrangement on cyclopropenes with low degrees of functionality around the three-membered carbocycle, they showed that a tertiary centre of this nature could be formed in only a few minutes at room temperature. On the other hand, Rubin and co-workers explored a range of functionalities around the cyclopropene ring and were, in most cases still able to drive the rearrangement to completion in moderate to excellent yields. Again, Marek observed a dominance of the *E*-isomer across all examples, while it was noted by Rubin that the diastereoselectivity of the reaction was governed by the electronics of the substituents present on the carbocycle (i.e. When R^1 was an electron withdrawing group, **69** was formed, yet when R^1 is an electron donating group **68** was formed).



Scheme 12: *Marek and Rubin's [2,3]-sigmatropic rearrangements of cyclopropenylalkylphosphinites*

The importance of the above syntheses demonstrates the rapid functionalisation and inclusion of heteroatom substituents into a three-membered carbocycle. The importance of oxygen, phosphorous and nitrogen containing three-membered carbocycles is greatly demonstrated biologically as it has been observed that both natural and synthetic cyclopropanes, containing heteroatoms, exhibit a broad range of biological properties including antibiotic, antifungal, antiviral and antitumour activities, as well as neurochemical activities, enzyme inhibition and promoting plant growth.[5,41] As examples of these compounds the cyclopropylurea **70**, synthesised initially by Hõgberg and co-workers,[42] has shown potent activity against HIV while *trans*-2-phenylcyclopropylamine (tranylcypromine) (**71**) is an irreversible inhibitor of monoamine oxidase and is used as a drug to treat a range of mental illnesses (Figure 4).[43]

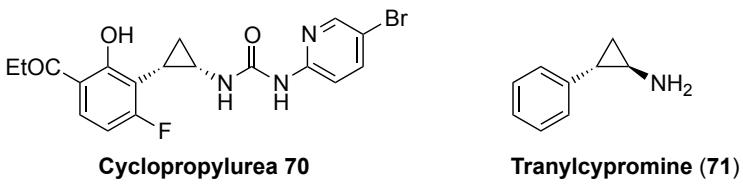


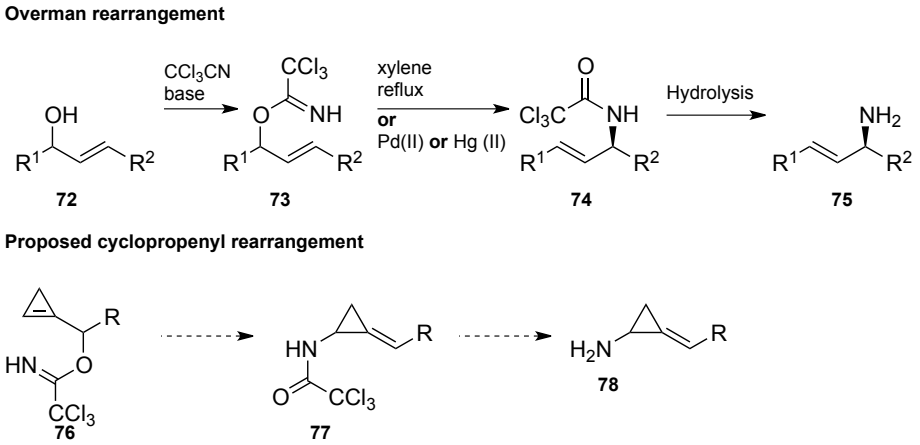
Figure 4: *Two examples of biologically relevant cyclopropylamines*

While there are well-developed methods for the synthesis of oxygen and phosphorous containing three-membered alkylidenecyclopropanes, there is currently no general method for the synthesis of the analogous nitrogen-containing alkylidenecyclopropanes. Conceptually, *N*-substituted alkylidenecyclopropanes can act as precursors for densely functionalised cyclopropylamines and cyclopropylureas, which as discussed are of biological significance and as such research to develop such a method is of high importance.

As seen from examples above, a common strategy for producing densely functionalised alkylidenecyclopropanes is from an intermolecular or intramolecular nucleophilic displacement of a cyclopropene. Heteroatom examples have been seen to work well from intramolecular rearrangements, and as such it is postulated that a similar intramolecular rearrangement containing a nitrogen nucleophile would be key to readily producing nitrogen-containing alkylidenecyclopropanes. A reaction that could facilitate this process is known as the Overman rearrangement.

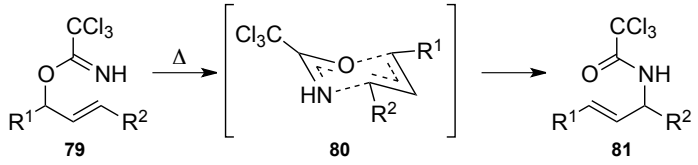
6.3 Overman rearrangement and proposed hypothesis

The [3,3]-sigmatrophic rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides, or the Overman rearrangement, is one of many sigmatropic rearrangements exploited in organic synthesis. Reported by Overman in 1974, the reaction involves first producing an allylic trichloroacetimidates (**73**) from the coupling of an allylic alcohol (**72**) with trichloroacetonitrile (Scheme 13a).[44,45] This carboximidate can then undergo rearrangement either thermally or with a transition metal to produce an allylic trichloroacetamide (**74**), which in turn can be reduced to reveal an allylic amine (**75**). It is postulated that the Overman rearrangement could be used for the production of cyclopropyl trichloroacetamides, which in turn could serve as precursors for relevant nitrogen substituted cyclopropanes (Scheme 13b).



Scheme 13: *a.) The general reaction for the Overman rearrangement; and b.) The proposed cyclopropenylmethyl trichloroacetimidate rearrangement*

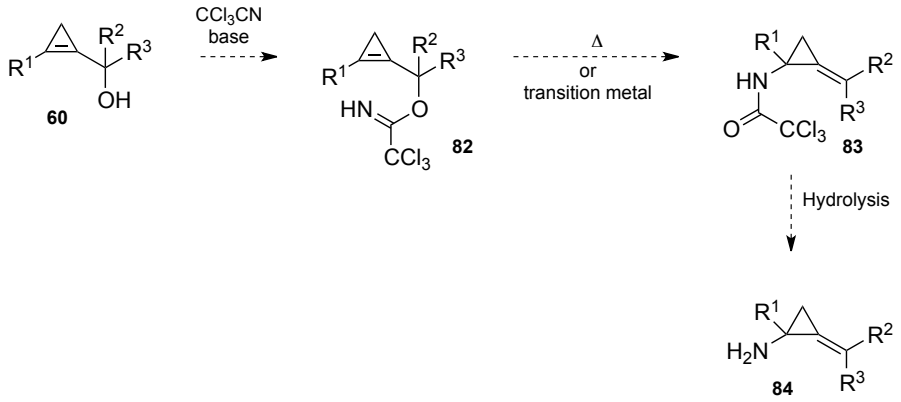
Typically, the Overman rearrangement requires high temperatures to proceed, undergoing a thermal [3,3]-sigmatropic rearrangement analogous to the Claisen rearrangement. However, the rearrangement can also be promoted at low temperatures by a mercury or palladium catalyst, and even enantioselectively with the appropriate catalyst.[46,47] The thermal rearrangement goes through a concerted mechanism where the nitrogen of the trichloroacetimidate attacks the alkene, which simultaneously shifts position while eliminating the oxygen leaving-group (Scheme 14). This irreversible process requires a high level of energy to proceed and it commonly performed in xylenes at reflux (~140 °C), however if one was to consider the high ring strain observed within the cyclopropene ring then the rearrangement might become energetically feasible due to relief of this strain and without the need for a metal catalyst.



Scheme 14: *Mechanism of the thermally promoted Overman rearrangement*

As seen by the collective research published by Fox, Marek and Rubin, using the strain energy of a cyclopropene to promote the rearrangement to an alkylidenecyclopropane is a realistic and practical pathway. The allylic trichloroacetimidates that are used for the Overman rearrangement are all derived from the analogous allylic alcohol, so it is postulated that a cyclopropenyl

trichloroacetimidate could be produced from a cyclopropenylcarbinol (Scheme 15). Furthermore, it is hypothesised that the Overman rearrangement to produce the key cyclopropyl amide **83** can proceed at lower temperatures than is typically observed due to the thermodynamic drive for the alleviation of ring strain. Thus, the following chapter will investigate locating optimal reaction conditions to produce cyclopropenyl trichloroacetimidates (**82**) from the cyclopropenylcarbinols (**60**), followed by testing whether the rearrangement can be promoted by the added strain energy of the cyclopropene at lower temperatures. If this chemistry proceeds, it will provide a powerful tool to generate cyclopropyl amide and cyclopropyl amine containing molecules; a process that is presently absent within the literature.

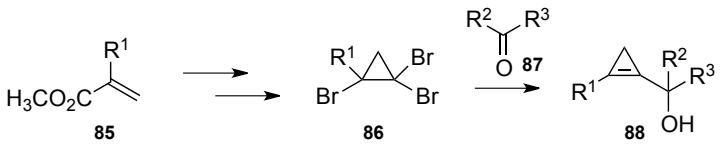


Scheme 15: *Proposed synthetic pathway to address the hypothesis*

Chapter 7 – Discussion

7.1 Synthesis of cyclopropenylcarbinol library

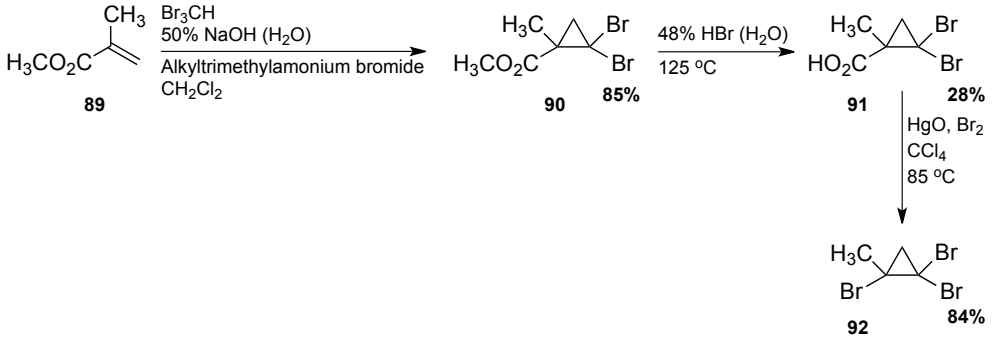
Previous work undertaken at the California State University (Amin, MSc 2009) had provided initial leads into the strain driven Overman rearrangement on the cyclopropenylcarbinol system. As part of a previous research project, a reliable method for the racemic synthesis of the starting cyclopropenylcarbinol scaffold had been identified and used successfully. The synthesis of the racemic cyclopropenylcarbinol starting materials was performed in two parts; firstly in producing the common intermediate 1,2,2-tribromo-1-methylcyclopropane,[48] and secondly synthesising a range of aryl substituted cyclopropenylcarbinols from this common intermediate (Scheme 16).[38]



Scheme 16: *Literature precedent for the preparation of a library of cyclopropenylcarbinols*

The synthesis of 1,2,2-tribromo-1-methylcyclopropane (**92**) from methyl methacrylate (**89**) was accomplished in an overall 20% yield over three steps (Scheme 17). This was achieved by first reacting methyl methacrylate (**89**) with dibromocarbene, which was generated *in situ* from the deprotonation of bromoform with sodium hydroxide, to produce the cyclopropyl methylester **90** in an 85% yield. This cyclopropyl methyl ester (**90**) was subsequently hydrolysed with concentrated hydrobromic acid (48% in H_2O) heated at reflux to yield the cyclopropyl carboxylic acid **91**. Curiously, the yield of this straightforward hydrolysis was only 28%, which was considerably lower than the 77% yield observed within the literature.[48] As a practical consideration, on the work-up of the reaction, the hydrolysis produced a brown oil that was left to sit and solidify overnight to reveal the pure solidified product. While a colourless solid was produced and collected by filtration, the mother liquor was never examined for further product, and the lower observed yield is likely due to poor crystallisation. This reaction was only performed once on a large scale and it was deemed impractical to go back and investigate the reaction further as enough material was obtained. With the cyclopropyl carboxylic acid (**91**) in hand, it

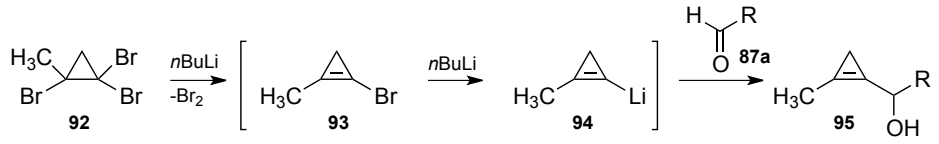
was treated with HgO and molecular bromine in carbon tetrachloride heated at reflux in a Hunsdiecker bromodecarboxylation to yield gram quantities of 1,2,2-tribromo-1-methylcyclopropane (**92**), which was used to synthesise all of the following cyclopropenylcarbinols.



Scheme 17: *The synthetic sequence to 1,2,2-tribromo-1-methylcyclopropane*

The spectra obtained for 1,2,2-tribromo-1-methylcyclopropane (**92**) matched that within the literature.[48] In the ^{1}H NMR spectrum there were two sets of doublets at 1.84 ppm and 1.94 ppm integrating for a single proton each. These two resonances were coupled to each other with a coupling constant of 9.2 Hz, which was consistent with that expected for two protons on the same carbon of a cyclopropane ring.[49] Further to this, a singlet integrating for three protons at 2.08 ppm was observed which was characteristic of a methyl group.

With a large stock of the common intermediate in hand, a well-established literature method by Marek and co-workers was followed to produce a diverse range of cyclopropenylcarbinol analogues on coupling an aldehyde (**87a**) with 1,2,2-tribromo-1-methylcyclopropane (**92**).[38] This was achieved by treating 1,2,2-tribromo-1-methylcyclopropane (**92**) with 2 equivalents of *n*-BuLi, followed by an aldehyde. Mechanistically, the first equivalent of *n*-BuLi performed a lithium halogen exchange, followed by elimination to produce the intermediate bromocyclopropene **93**. A second metal-halogen exchange was achieved by the second equivalent of *n*-BuLi generating the highly reactive organolithium intermediate **94**, which was subsequently captured by an aldehyde (**87a**) to produce the cyclopropenylcarbinol (**95**) (Scheme 18).



Scheme 18: *The synthesis of cyclopropenylcarbinols*

The synthesis of the cyclopropenylcarbinols (**95**) was performed with a range of aromatic aldehydes with a variety of substitution patterns and functional groups. This produced a good range of cyclopropenylcarbinols in moderate to excellent yields with electron withdrawing and electron donating functionalities ideal for testing the hypothesised rearrangement (Table 1). The cyclopropenylcarbinols were primarily identified by the diagnostic resonance in the ^{1}H NMR spectrum of the proton adjacent the newly installed alcohol. This resonance typically appeared as a broad singlet between 5.50 ppm and 6.00 ppm. Further to this, as with the 1,2,2-tribromo-1-methylcyclopropane (**92**) starting material, two sets of doublets coupled to each other integrating for a single proton each were observed at approximately 1.01 ppm and at 1.05 ppm in all substrates. Interestingly, the methyl group substituted on the cyclopropene ring was observed as a doublet with a small coupling constant of approximately 1.5 Hz, which suggested long range coupling across the alkene bond to the proton adjacent the newly installed alcohol (Figure 5). Furthermore, the presence of two diagnostic cyclopropene resonances in the ^{13}C NMR at approximately 110 ppm and 111 ppm gave sufficient evidence for cyclopropene production.[49]

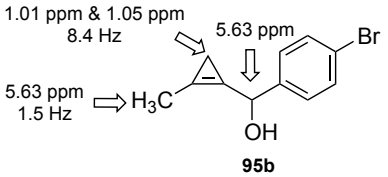
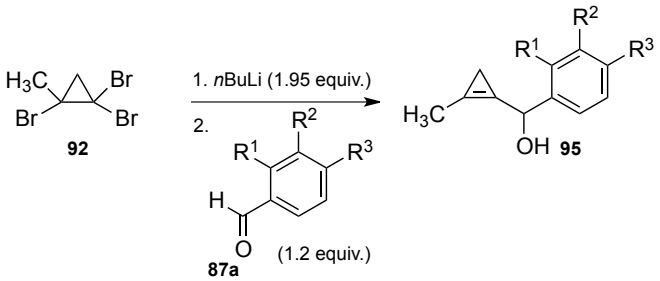


Figure 5: *Assignment of the resonances observed within the ^{1}H NMR spectrum of cyclopropenylcarbinol* ***95b***

It was observed that as the electron density of the aromatic ring increased the yield of the resulting cyclopropenylcarbinol decreased. This is likely due to partial electronic donation from the electron rich aromatic system to the aldehyde carbonyl, reducing the partial positive charge on the carbon of the aldehyde carbonyl making it less

reactive with the nucleophilic organolithium intermediate. The lower isolated yield was also likely a result of the electron rich analogues instability on silica.

Table 1: *The range of cyclopropenylcarbonols synthesised*

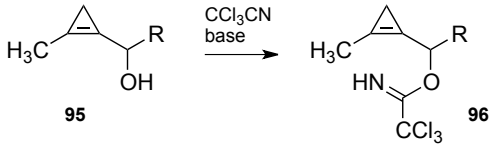


Cyclopropenylcarbinol	R_1	R_2	R_3	Yield
95a	-H	-H	-H	48%
95b	-H	-H	-Br	87%
95c	-H	-H	$-OCH_3$	64%
95d	-H	-H	$-CH_3$	60%
95e	-H	-H	$-NO_2$	94%
95f	-H	$-NO_2$	-H	87%
95g	-H	$-OCH_3$	-H	30%
95h	-Cl	-H	-H	99%
95i	Aldehyde = *N*-Tosylpyrole-2-carboxyaldehyde			29%

7.2 Investigation into the Overman rearrangement

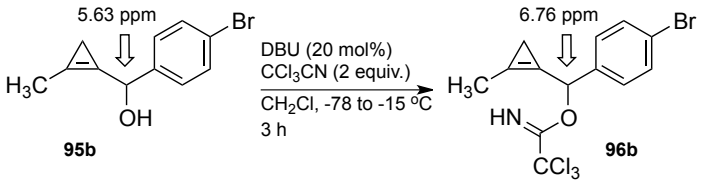
With a selection of cyclopropenylcarbinols in hand, investigations into the allylic trichloroacetimidate rearrangement began, focusing primarily on the *p*-bromobenzaldehyde derived cyclopropenylcarbinol **95b** to probe reactivity and develop optimal conditions (Scheme 19). Initial investigations concentrated on exploring conditions for the thermal rearrangement of the allylic system. Probing the capacity for rearrangement without a transition metal catalyst would address the primary hypothesis that the alleviation of the high strain energy found in the

cyclopropene ring would be enough of a thermodynamic drive to promote the reaction to the proposed benzylidenecyclopropane.



Scheme 19: *Proposed synthesis of cyclopropenyl trichloroacetimidates from cyclopropenylcarbinols*

Being aware that uncontrolled rearrangement could happen if reaction temperatures were too high, attempts to synthesise the cyclopropenyl trichloroacetimidate were performed at low temperatures to try to avoid this outcome. As per general literature procedures, the *p*-bromobenzaldehyde derived cyclopropenylcarbinol **95b** was treated with DBU and trichloroacetonitrile (CCl_3CN) in CH_2Cl_2 at −78 °C for 4 h. After this time, the reaction was worked-up by adding H_2O and extracting with CH_2Cl_2 to produce a crude mixture, mainly consisting of cyclopropenyl trichloroacetimidate **96b**. On modification, optimal reaction conditions for the synthesis of cyclopropenyl trichloroacetimidate **96b** involved treating cyclopropenylcarbinol **95b** with a catalytic amount of DBU (20 mol%) in dry CH_2Cl_2 at −78 °C, followed by the addition of CCl_3CN and warming to a maximum of approximately −15 °C over 3 h (Scheme 20). After this time the reaction mixture was put under reduced pressure to evaporate the volatiles to yield clean cyclopropenyl trichloroacetimidate **96b** quantitatively. This reaction went to completion over this time in all cases giving an essentially quantitative mass recovery. Purification of these intermediate cyclopropenyl trichloroacetimidates to obtain accurate yields was not performed after initial attempts of purification resulted in extensive decomposition, and as such they were used without purification.



Scheme 20: *Reaction conditions for the synthesis of the intermediate trichloroacetimidate for the proposed Overman rearrangement*

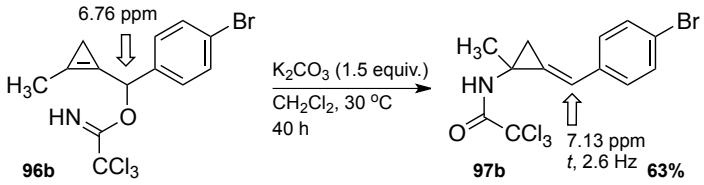
Trichloroacetimidate **96b** was primarily identified in the ^{1}H NMR spectrum by the shift of the singlet assigned as the proton adjacent to the hydroxyl functional group in cyclopropenylcarbinol **95b** from 5.63 ppm, downfield to 6.76 ppm for trichloroacetimidate **96b**. Further to this, a new resonance at 8.43 ppm was identified, which was assigned as that of the imine proton. As with that observed for the cyclopropenylcarbinol starting material, there were two doublets coupled to each other integrating for one proton each at 1.06 ppm and at 1.14 ppm, which were assigned as the protons on the cyclopropene ring. Also, the resonances assigned to the methyl group substituted on to the ring was still split as a doublet with a small coupling constant, as was observed for the starting material suggesting similar long range coupling between the methyl group and the proton adjacent to the imidate.

In an attempt to identify alternative reaction conditions, different bases for the initial alcohol deprotonation were briefly investigated. However, it was observed that the use of different bases such as NaH, KH and *n*-BuLi only resulted in recovered starting material. It was also found that the reaction could not be left longer than 3 h or allowed to warm to room temperature. Longer reaction times and warmer conditions led to decomposition of the reaction mixture and, in some instances, partial rearrangement through to the allylic trichloroacetamide (**87**). This gave an early indication that on further optimisation the rearrangement would proceed as desired. As an added precaution, the volatiles were carefully evaporated under reduced pressure without heating the water bath of the rotary evaporator above room temperature.

With an efficient synthesis of the allylic trichloroacetimidate in hand, attention was turned to towards identifying optimum conditions for the Overman rearrangement. As already alluded to above, in some of the early attempts at identifying conditions for the synthesis of the allylic trichloroacetimidate, the amide had been observed suggesting that the rearrangement could occur under mild thermal conditions. With this lead, allylic trichloroacetimidate **96b** was stirred in dry CH_2Cl_2 overnight at room temperature. From this, it was observed that allylic trichloroacetimidate **96b** underwent the proposed [3,3]-sigmatropic rearrangement under very mild conditions to yield a single geometric isomer of cyclopropylamide **97b**, albeit in lower than an acceptable yield (sub ~10%). As proposed, due to the strain energy of the ring the rearrangement could be achieved at lower temperatures than are usually associated

with this allylic rearrangement (often as high as 140 °C). On optimisation of the reaction conditions the allylic trichloroacetimidate was heated in CH_2Cl_2 at 30 °C for 40 h to promote the rearrangement further, increasing the yield to 21% after purification.

It has been reported that bases were often used in conjunction with the Overman rearrangement to limit decomposition from the acidic environment generated during the rearrangement,[50] and as such the 2-step yield of the reaction was found to significantly increase from 21% with out any additive to 63% with 1.5 equivalents of K_2CO_3 added to the reaction mixture (Scheme 21). As a quick test of whether an improvement would be achieved under the standard transition-metal mediated rearrangement, $PdCl_2(CH_3CN)_2$ was added to the reaction mixture in CH_2Cl_2 at 30 °C for 40 h (Table 2). This test reaction resulted in a crude mixture consisting of numerous unidentified decomposition products, with only a trace of the desired amide being observed; as such the catalytic pathway was not pursued further.



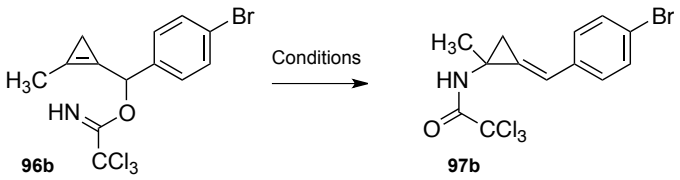
Scheme 21: *Reaction conditions for the synthesis of allylic amide*

Evidence of the formation of trichloroacetamide **97b** was observed in the ^{1}H NMR spectrum from the diagnostic shift from 6.76 ppm of the proton adjacent to the trichloroacetimidate to a triplet at 7.13 ppm, assigned as the exocyclic alkene. The triplet for the exocyclic alkene of the benzylidenecyclopropane, was observed to be coupled to the two allylic protons attached to the carbon of the cyclopropane ring with a coupling constant of 2.6 Hz. This was supported by the two resonances that were assigned as the protons in the cyclopropane ring, which now appeared as two doublet of doublets. The coupling constants for these resonances were 2.6 Hz and 10.9 Hz, with the former being that coupling with the exocyclic alkene proton and the later being of appropriate magnitude for two protons on a single carbon within a cyclopropane.[49] Further evidence that supported the formation of the amide was observed in the up field shift of the nitrogen bound proton of the trichloroacetimidate from 8.43 ppm to 7.07 ppm in the amide. The methyl that was substituted at the

alkene of the cyclopropene, which presented as a doublet in the trichloroacetimidate, had collapsed down to a singlet in the amide, which is likely due to loss of the long range coupling seen previously. In addition to the ^{1}H NMR spectrum, extra evidence for formation of the amide was observed within the ^{13}C NMR spectrum with a carbonyl carbon resonance present at 162.3 ppm as well as a carbonyl stretch observable in the IR spectrum at 1693 cm^{-1}.

The rearrangement of the *p*-bromobenzaldehyde derived cyclopropenylcarbinol **95b** took a minimum of approximately 40 h as reactions ran for less time proved to be much lower yielding of the desired amide. These conditions were optimal however, as heating the reaction mixture to reflux in CH_2Cl_2 led to decomposition. Furthermore, while changing the solvent to DMF did increase the rate of the reaction (Table 2), a lower yield of 53% was obtained.

Table 2: *Summary of conditions trialled for the rearrangement of allylic trichloroacetimidate* ***84b***

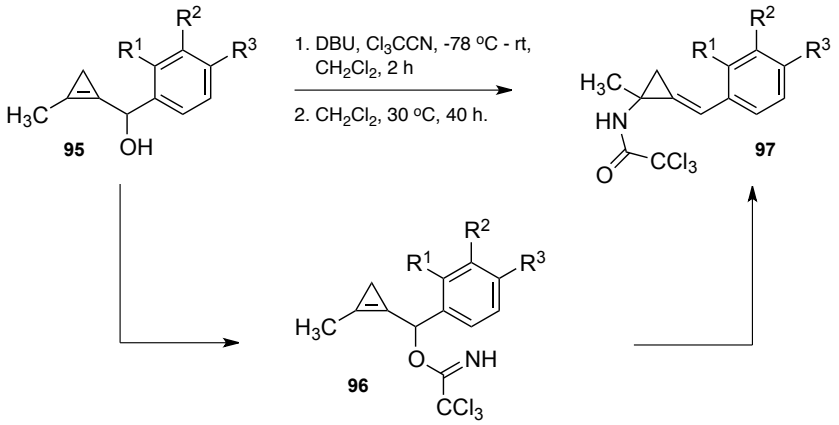


Entry	Additive	Conditions	Time	Yield
1	None	30 °C, CH_2Cl_2	40 h	21%
2	K_2CO_3 (1.5 equivalents)	30 °C, CH_2Cl_2	40 h	63%
3	$PdCl_2(CH_3CN)_2$ (0.05 equivalents)	30 °C, CH_2Cl_2	24 h	<5%
4	K_2CO_3 (1.5 equivalents)	30 °C, DMF	22 h	53%

A range of different aryl-substituted cyclopropenyl trichloroacetimidates were subjected to the rearrangement conditions (Table 3). As with what was observed with the cyclopropenylcarbinols, the electronic properties of the aromatic rings played a significant role in the yield of the reaction. It was observed that those trichloroacetimidates containing electron rich aryl groups underwent rearrangement

far more efficiently than those with electron poor aryl groups, which was in contrast to the electron poor analogues outperforming the electron rich analogues in the initial synthesis of the cyclopropenylcarbinols. Interestingly, highly electron-deficient nitro-substituted aryl systems did not undergo rearrangement at all and just provided recovered starting material, even at high temperatures. It was likely then that the electron-deficient aryl groups were likely disfavouring the development of positive charge in the transition state at the benzylic carbon. This observation, coupled with the higher reactivity of electron-rich aryl groups, suggests the possibility of a transition state with partial ionic character.

Table 3: *A library of substrates subjected to the rearrangement*



Entry	R_1	R_2	R_3	Yield
97a	-H	-H	-H	83%
97b	-H	-H	-Br	63%
97c	-H	-H	$-OCH_3$	77%
97d	-H	-H	$-CH_3$	98%
97e	-H	-H	$-NO_2$	0%
97f	-H	$-NO_2$	-H	0%
97g	-H	$-OCH_3$	-H	47%
97h	-Cl	-H	-H	48%
97i	Aldehyde = *N*-Tosylpyrole-2-carboxyaldehyde			99%

All of the produced amides were obtained as the *E*-isomers, which was assigned through observed nOe correlations between the alkene proton and the protons of the methyl carbon, suggesting the proton of the alkene was on the same side of the alkene as the methyl group (Correlation A, Figure 6). Further to this, there was a strong observed nOe correlation between the two protons of the cyclopropane ring and a proton in the aromatic ring of the *o*-chloro analogue **97h**, which gives evidence

that the aromatic functionality is on the same side of the alkene as the two protons of the cyclopropane (Correlation B, Figure 6). A noticeable feature of the NOSEY spectrum is the strong COSY breakthrough that is observed between the benzylidene proton and the cyclopropane protons, which is sometimes seen in compounds that have strong COSY correlations. It should be noted that there was no evidence of an nOe correlation between the amide proton and the benzylidene proton.

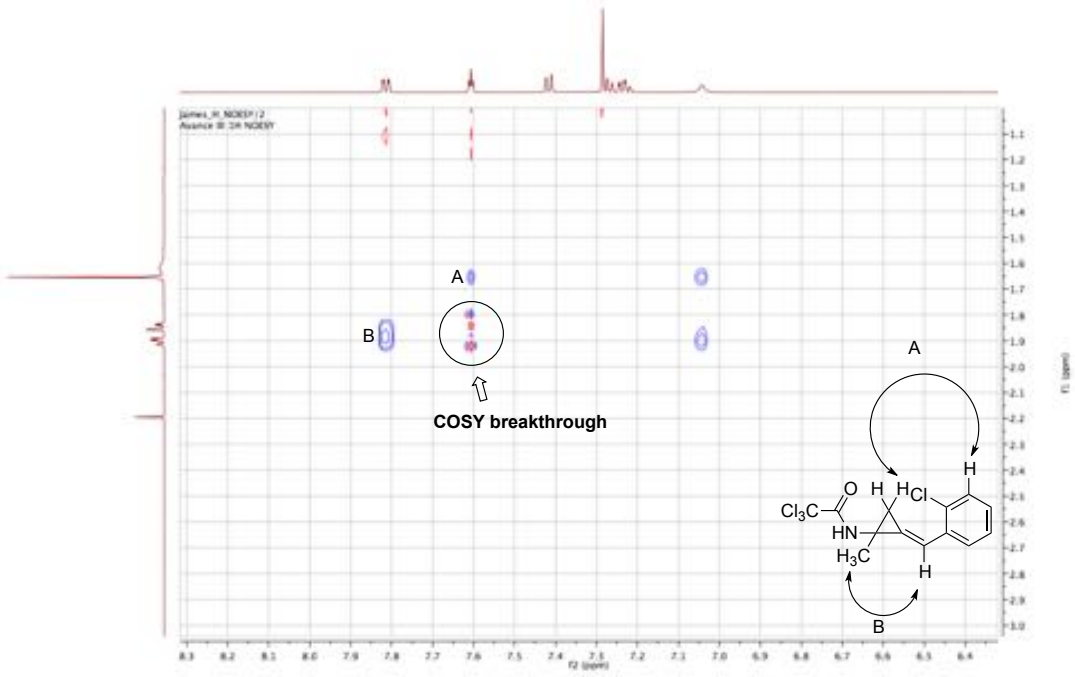
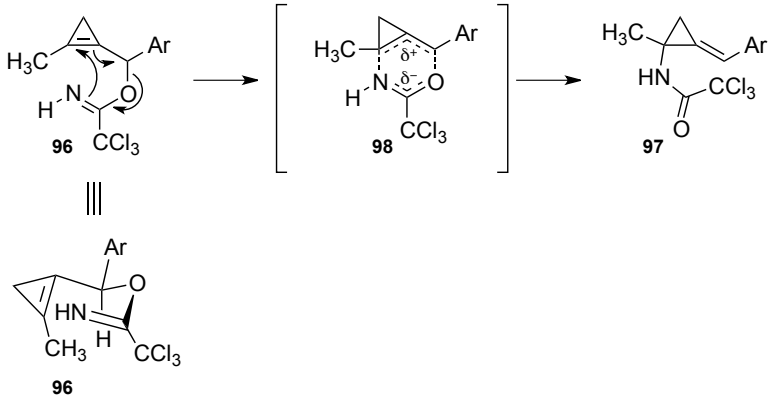


Figure 6: *NOSEY spectra for cyclopropyl trichloroacetamide* ***87h***

Due to the exclusive formation of the *E*-isomer in the reaction it is likely that, as with typical Overman rearrangements, the rearrangement of the cyclopropenyl trichloroacetimidates likely proceeds through a concerted [3,3]-sigmatropic rearrangement mechanism. Furthermore, it has been discussed that the transition state **98** likely possesses a partial positive charge across the all carbon fraction of the molecule, with a partial negative charge across the $HNC(CCl_3)O$ fraction (Scheme 22).[51] This would help explain the lack of reactivity of those analogous with electron deficient aryl functionality, as they would disfavour the development of the partial positive charge required for reactivity. In analogy to that proposed by Marek and co-workers for the mechanism of the rearrangement of cyclopropenyl acetates (Scheme 11),[39] it was believed that the rearrangement of **96** proceeded through a pseudo-chair transition state conformation that had the aromatic functional group in the pseudo-

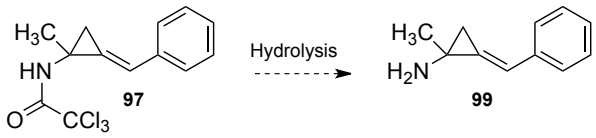
equatorial position due to steric influences. With the aromatic functional group in the pseudo-equatorial position, when the alkene shift occurs it would be forced to have the *E*-geometry rather than the *Z*-geometry that would be obtained from the aromatic functional group being in the pseudo-axial position, a result that was highly unfavourable due to steric effects keeping the hydrogen atom in the pseudo-axial position.



Scheme 22: *The suggested mechanism of the allylic trichloroacetimidate rearrangement*

7.3 Manipulation of the cyclopropyl trichloroacetamide

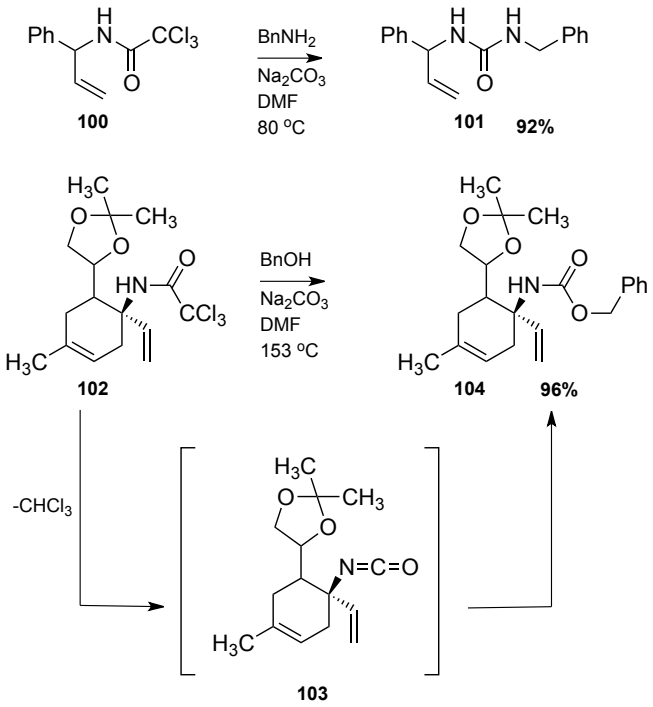
As a secondary aim to this project, the free benzylidenecyclopropyl amine (**99**) was a target, as it would provide a unique synthesis for a library of analogues of highly biologically active small molecules, analogous to such compounds as tranylcypromine.



Scheme 23: *Proposed reduction for the cleavage of the trichloroacetamide functional group*

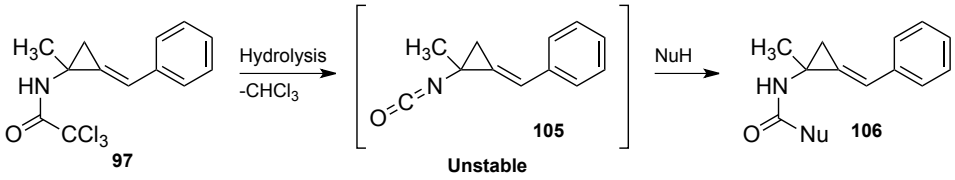
Trichloroacetamides are commonly hydrolysed to the corresponding amine under standard acid or base hydrolysis conditions.[50] Thus, acid hydrolysis in 1 M HCl at 0 °C was attempted as well as base assisted hydrolysis with KOH in EtOH. Both of these attempts failed to deliver the desired amine, and in both cases starting material was recovered along with uncharacterised decomposition products. Reductive cleavage of the allylic trichloroacetamide was also attempted using DIBAL-H and also $NaBH_4$, however these attempts also resulted in a complex mixture of

uncharacterised decomposition products. These results were attributed to an unstable isocyanate intermediate, similar to those observed by Isobe and co-workers who reported similar difficulties converting trichloroacetamides **100** and **102** to the parent amine (Scheme 24).[52-54]



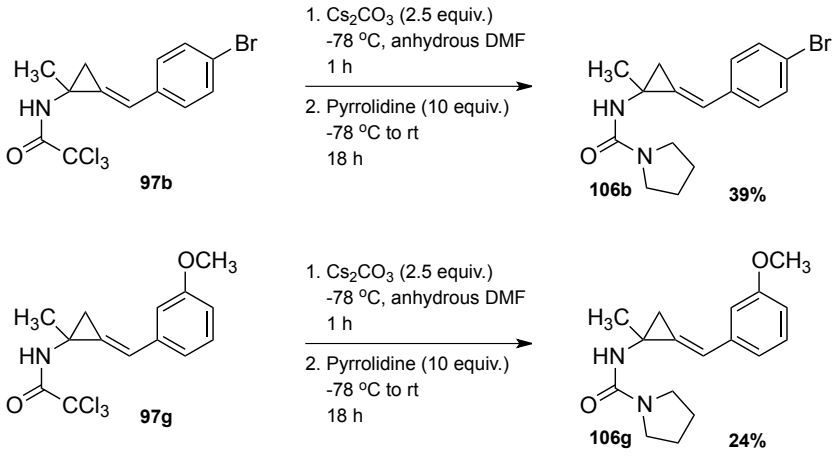
Scheme 24: *Two examples of the generation of the isocyanate intermediate followed by capture with a nucleophile by Isobe and co-workers*

To get around the instability of the unstable isocyanate intermediate that was produced on initial cleavage of the trichloroacetamide, Isobe and co-workers devised a strategy where a nucleophile was introduced into the reaction mixture. This resulted in an *in situ* nucleophilic capture of the intermediate isocyanate producing functionalised ureas or cabamates depending on the added nucleophile. As the direct conversion of the cyclopropyl trichloroacetamides to the proposed amines was unsuccessful a similar strategy to that of Isobe's was employed (Scheme 25). If successful, this strategy would result in cyclopropyl ureas similar to those reported by Högberg and co-workers that show significant anti-HIV activities,[42] and those cyclopropyl ureas reported by Howard and co-workers that act as kinase inhibitors.[55]



Scheme 25:*Proposed redesign in an attempt to remove the trichloromethane*

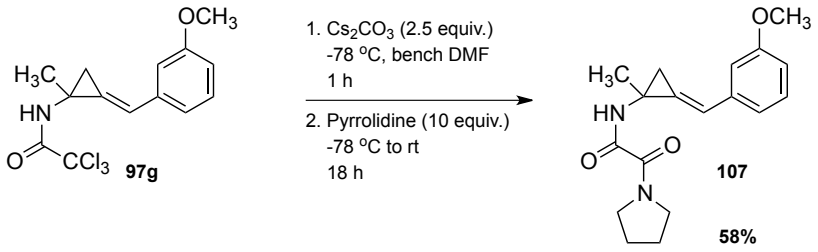
Cyclopropyl trichloroacetamide **97b** was treated with Cs_2CO_3 in DMF at −78 °C for 1 h to generate the proposed isocyanate intermediate. After this time, the reaction mixture had an excess of pyrrolidine added to it, which was chosen due to its strong nucleophilicity. The reaction was left to stir at room temperature overnight to produce cyclopropyl urea **106b** in a 39% yield after purification, with no by-products being identified in the ^{1}H NMR spectrum of the crude material. This un-optimised reaction worked well to give evidence for the intermediate isocyanate forming and was also performed on cyclopropyl trichloroacetamide **97g** to produce cyclopropyl urea **106g** in a 24% yield (Scheme 26). The urea containing molecules were identified primarily in the ^{1}H NMR with the proton attached to the nitrogen of the amide shifting up field by approximately 0.5 ppm due to removing the shielding effects of the three chlorines. Further to this, the diagnostic *N*-substituted pyrrolidine resonances were observed in both ^{1}H NMR spectra with a multiplet integrating for four protons observed between approximately 1.74 ppm and 1.78 ppm, with a further two sets of two multiplets integrating for two protons each at approximately 2.41 ppm to 2.47 ppm and 2.68 ppm to 2.72 ppm.



Scheme 26: *The non-optimised capture of the isocyante intermediate with pyrrolidine*

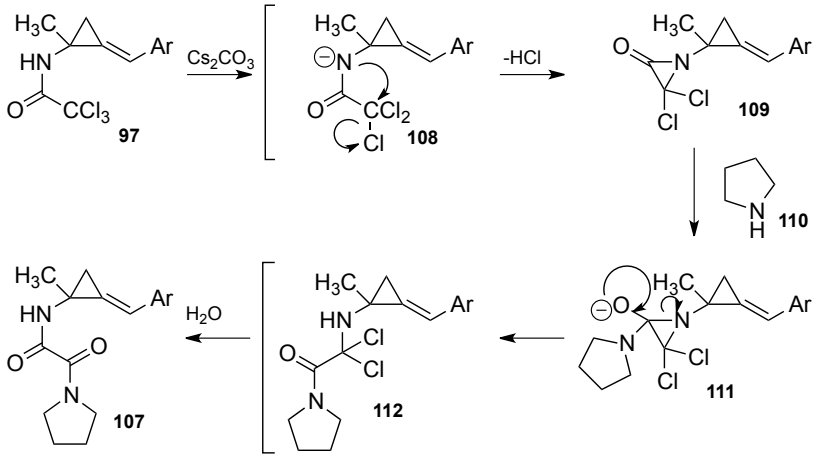
An interesting outcome was observed when bench grade DMF was used over anhydrous DMF. Using bench grade DMF cyclopropyl oxoacetamide **107** was

produced in a 58% yield (Scheme 27). Such a result was unexpected, however, has been observed in the literature by Braverman and co-workers as well as De Kimpe and colleagues.[56,57]



Scheme 27: *The unexpected outcome of using non-anhydrous DMF*

While it was not entirely clear as to why cyclopropyl oxoacetamide **107** was the sole product when water was present in DMF and why urea **106** was only observed under anhydrous conditions, a mechanism resembling a Favorskii rearrangement has been suggested for this pathway (Scheme 28). As proposed by Braverman and co-worker, due to the basic conditions, the nitrogen of the amide can be deprotonated and attack the carbon of the carbonyl, eliminating HCl to generate the dichloroaziridinone intermediate **109**.[56] The carbon of the carbonyl can be subsequently attacked by the pyrrolidine nucleophile (**110**) before ring opening and hydrolysis to yield the second carbonyl of oxoacetamide **107**.

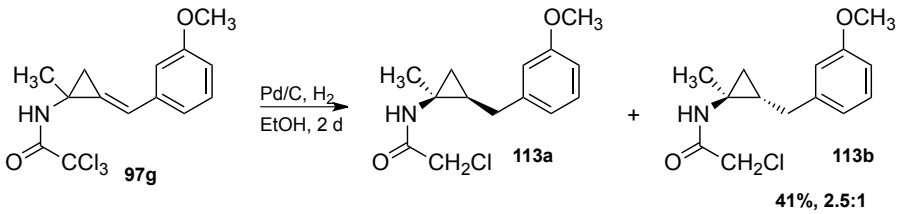


Scheme 28: *Literature proposed mechanism for the formation of the cyclopropyl oxoacetamide*

While the proposed mechanism was reported in the literature, it seemed unlikely as the water was proposed to only act in the last step. For this mechanism to hold true,

the reaction performed under anhydrous conditions would not produce the urea functionality as observed, rather producing a dichloro-compound analogous to **112** (Scheme 28). It is likely then that a different mechanism was taking place where water acts as a nucleophile earlier in the reaction.

Along with attempts to convert the trichloroacetamide to the amine, hydrogenation to reduce the alkene to the parent cyclopropane was also attempted given the biological significance of nitrogen-substituted cyclopropanes. The catalytic hydrogenation of racemic cyclopropyl trichloroacetamide **97g** took place with Pd/C under an atmosphere of H_2 in ethanol to initially produce a complex reaction mixture of various reduction products. The major compound was identified as monochloro amide **115** as the hydrogenation conditions were suitable to reduce both the alkene as well as the halogen bonds. In extending the reaction time to two days, only monochloro amide **113** was produced in 41% yield; with the low reaction yield being attributed to the *in situ* generation of HCl potentially decomposing reactants and products. While not examined, a consequence of this reduction is the remaining chlorine atom that could be used as a convenient synthetic handle in further reactions. This could be used to build more functionality into the molecules with substitution reactions or various coupling reactions.



Scheme 29: *Catalytic hydrogenation of racemic cyclopropyl trichloroacetamide* ***97g***

The reduction produced a mixture of diastereomers that were primarily identified as the monochloro amides **113a** and **113b** by analysis of the ^{1}H NMR spectrum. For each compound there were two diastereotopic protons attached to the benzylic carbon. In both compounds these appeared as doublets of doublets, coupling to the newly introduced proton of the cyclopropane ring, with the major compounds resonances appearing at 2.62 ppm and 2.83 ppm and the minor compounds resonances appearing at 2.51 ppm and 2.93 ppm (Figure 7). Further to these resonances, the new resonances for the protons that displaced the chlorine atoms

appeared as singlets integrating for two protons each at 3.99 ppm for the minor compound and 4.03 ppm for the major compound. Through careful integrations of the ^{1}H NMR a ratio of 2.5:1 was calculated for the major compound to the minor compound. This bias towards compound **113a** suggests that H_2 is likely being preferentially delivered to the least hindered face of the cyclopropene (i.e. the opposite face to the trichloroacetamide).

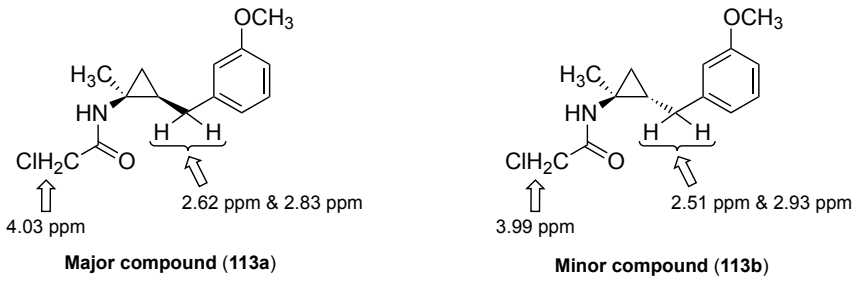


Figure 7: *The diagnostic proton assignments of the two monochloro amide diastereomers*

The configuration of the diastereomers was assigned through careful nOe observations and analysis. The two diastereomers were not separable from each other through standard silica gel flash chromatography so analysis was performed on the mixture of the compounds. The data obtained from the NOSEY spectrum was inconclusive so individual 1D nOe spectra were collected for each of the resonances. On selective irradiation of the benzylic proton resonances of the major compound **113a**, there was no evidence to suggest correlation between these resonances and the clear singlet resonance for the methyl of the cyclopropane ring, suggesting that the benzyl system and the methyl group were not on the same face of the cyclopropane ring for the major compound. However, on selective irradiation of the benzylic proton resonances of the minor compound **113b** this correlation was strong giving evidence that the benzylic functional group was on the same face as the methyl group on the cyclopropane ring.

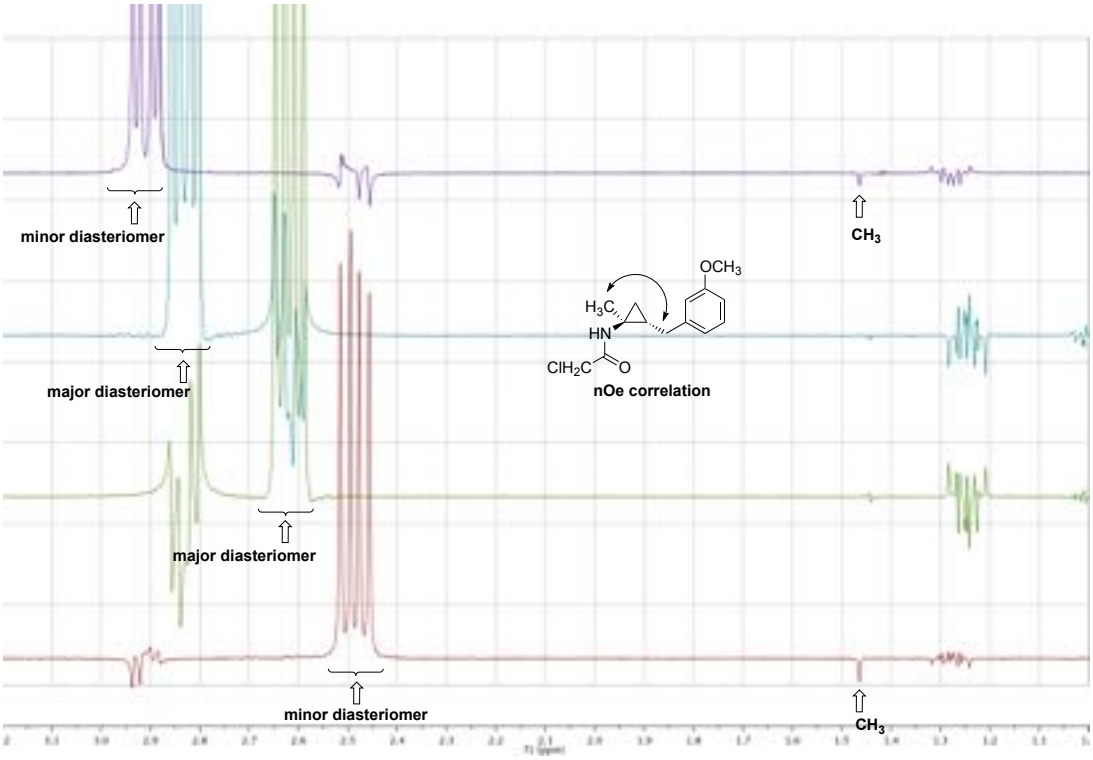


Figure 8: *1D nOe correlations between selectively pulsed benzylic protons and the methyl proton of the cyclopropane ring*

7.4 Summary and conclusion

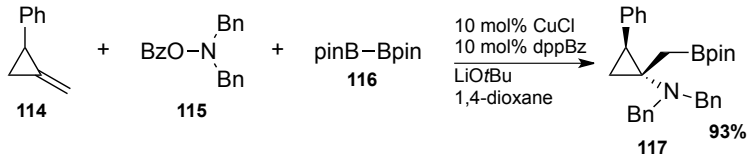
In summary, a method has been developed to produce a small library of benzylidenecyclopropyl trichloroacetamides *via* the allylic trichloroacetimidate rearrangement, or Overman rearrangement, under mild conditions – without the need for a catalyst.

A library of racemic cyclopropenylcarbinols were initially synthesised by following a known method before the coupling of trichloroacetonitrile was investigated to produce a library of cyclopropenyl trichloroacetimidates. This efficient coupling was found to occur rapidly at low temperatures with a catalytic amount of DBU to promote the reaction. These molecules rearranged at 30 °C in good to excellent yields in the first example of the Overman rearrangement on cyclopropenes. This rearrangement was promoted by the inherent strain energy within the cyclopropene ring and, as of yet demonstrates the only rearrangement of a cyclopropene to an alkylidenecyclopropane with a nitrogen atom participant.

As an example of the utility of the products of this rearrangement, two of the benzylidenecyclopropyl trichloroacetamides were further manipulated with reduction chemistries. Using a strategic modification of known chemistry, these molecules were transformed into biologically relevant benzylidenecyclopropyl ureas and monochloro cyclopropanes.

The synthesis of benzylidenecyclopropyl trichloroacetamides shown in this thesis is a valuable inclusion to the ever-growing area of alkylidenecyclopropane synthesis and adds more understanding to cyclopropene related chemistry. Further to this, it adds a new and novel strategy to the direct addition of a nitrogen atom to a tertiary carbon of a cyclopropane.

Future research into this area should focus on the enantioselective synthesis of benzylidenecyclopropyl trichloroacetamides from enantiomerically pure cyclopropenylcarbinols, which can be prepared in excellent yields from methodology by Marek and co-workers.[13] Furthermore, advanced synthesis on the benzylidenecyclopropyl trichloroacetamides needs to be achieved to cement it's utility as a molecular building block. The alkene moiety is perhaps the most obvious place to focus initial attempts, as the alkene should serve as a key synthetic handle for the introduction of carbon and sulfur nucleophiles, while also serving as a platform to introduce oxygen-containing functionalities into the molecule. An example of methodology that could be applied to the trichloroacetamides is the copper catalysed aminoboration reaction developed by Miura and co-workers (Scheme 31).[58] They apply this stereoselective methodology to range of methylenecyclopropanes, producing molecules containing a boryl moiety that can serve as a further synthetic handle. Methodology of this type will rapidly generate complex small molecules from the benzylidenecyclopropyl trichloroacetamides described above.



Scheme 30: *An example of Mirua and co-workers copper catalysed aminoboration methodology*

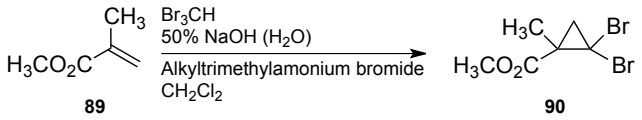
Chapter 8 – Experimental

8.0 General Experimental

See page 103 for the general experimental details.

8.1 Synthesis of 1,2,2-tribromo-1-methylcyclopropane

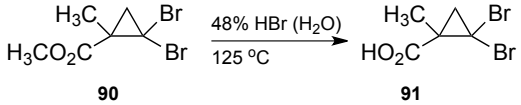
RS-2,2-Dibromo-1-methylcyclopropanecarboxylate (90)



To a solution of methyl methacrylate (**89**) (49.8 g, 0.49 mol), bromoform (156.1 g, 0.62 mol) and alklytrimethylamonium bromide (3.0 g, 9.0 mmol) in CH_2Cl_2 (150 mL) was slowly added a 50% solution of NaOH (100 g) at 0 °C. The resultant solution was allowed to stir for 20 h before an additional portion of bromoform (30 g, 0.12 mol) and NaOH solution (20 g) were added and the solution was left to stir for another 24 h. After this time H_2O (300 mL) was added to the reaction mixture before extraction with CH_2Cl_2 (3 x 100 mL), drying over $MgSO_4$, filtering and removing the solvent under reduced pressure. The oily residue was treated with pentane (150 mL) to reveal an off-white solid as the desired product **90** in 85% yield. The ^{1}H NMR spectrum agreed with literature values.[48]

^{1}H NMR (300 MHz, $CHCl_3$) δ 1.57 (d, J = 7.9 Hz, 1H), 1.60 (s, 3H), 2.42 (d, J = 7.9 Hz, 1H), 3.78 (s, 3H).

RS-2,2-Dibromo-1-methylpropanecarboxylic acid (91)

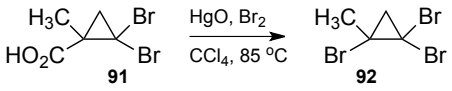


To a solution of HBr (48 %, 120 mL) was added 2,2-dibromo-1-methylcyclopropanecarboxylate (**90**) (27.2 g, 0.1 mol) and the resulting solution was heated at reflux for 5 h. The solution was then allowed to cool to rt before H_2O (200 mL) was added and the mixture extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried over

$MgSO_4$ and filtered before the solvent was removed under reduced pressure to yield a brown oil. On cooling the liquid mixture overnight, the title carboxylic acid **91** had solidified and was collected by vacuum filtration in a 28% yield (7.08 g, 27.5 mmol). The ^{1}H NMR spectrum agreed with literature values.[48]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.33 (m, 1H), 2.20 (d, J = 7.9 Hz, 1H).

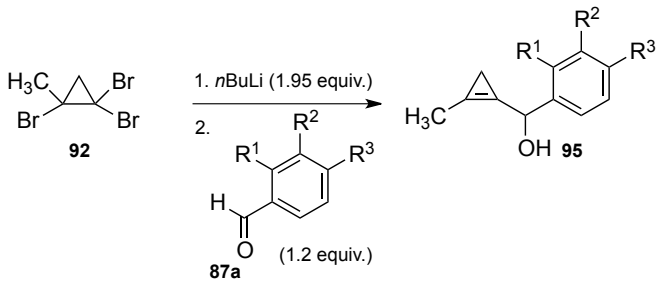
***RS*-1,2,2-tribromo-1-methylpropane (92)**



A mixture of 2,2-dibromo-1-methylpropanecarboxylic acid (**91**) (18.1 g, 70.3 mmol) and HgO (15.5 g, 73.6 mmol) in CCl_4 (100 mL) was refluxed at 85 °C before Br_2 (13.5 g, 84.3 mmol) in CCl_4 (25 mL) was added over a period of 30 min. The mixture was allowed to stir at reflux for 4 h before cooling to room temperature and stirring for a further 18 h. After this time the mixture was diluted with pentane (100 mL) before flushing through a short pad of silica and Celite®. The resulting mixture was purified by distillation to reveal the desired product **92** as a colourless oil in 84% yield (17.3 g, 59.1 mmol). The ^{1}H NMR spectrum agreed with literature values.[48]

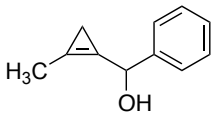
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J = 9.2 Hz, 1H), 1.98 (d, J = 9.2 Hz, 1H), 2.08 (s, 3H).

8.2 General procedure for the synthesis of cyclopropenylcarbinols



In an oven dried 2-neck flask was added 1,2,2-tribromo-1-methylpropane (**92**) (1.0 equiv.) and anhydrous Et_2O (20 mL) before cooling to −78 °C and adding *n*-BuLi (1.45 M, 1.9 equiv.). The resultant solution was warmed to −10 °C for 30 min before cooling to -50 °C and adding the selected aldehyde. The solution was warmed to room temperature after 10 min and left to stir for 2 h before quenching with H_2O (20 mL). The mixture was then extracted with Et_2O (3 x 20 mL), dried on Na_2SO_4 and filtered before the solvent was removed under reduced pressure. The crude oil was the purified by flash chromatography on silica gel treated with Et_3N (ethyl acetate: hexanes).

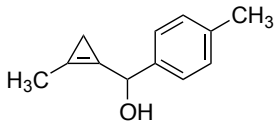
_RS_-(2-methylcycloprop-1-enyl)(phenyl)methanol (95a)



From benzaldehyde according to the general method in 48% yield after purification with 20% ethyl acetate: hexanes as a colourless oil. The ^{1}H NMR spectrum agreed with literature values.[38]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, *J* = 8.4 Hz, 1H), 1.07 (d, *J* = 8.4 Hz, 1H), 2.1 (d, *J* = 1.2 Hz, 3H), 5.68 (s, 1H), 7.28-7.43 (m, 5H).

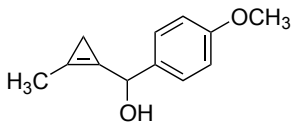
***RS*-(2-methylcycloprop-1-enyl)(4-methylphenyl)methanol (95d)**



From 4-methylbenzaldehyde according to the general method in 60% yield after purification with 20% ethyl acetate: hexanes as a colourless oil. The ^{1}H NMR spectrum agreed with literature values.[38]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J* = 8.4 Hz, 1H), 1.05 (d, *J* = 8.4 Hz, 1H), 2.09 (d, *J* = 1.5 Hz, 3H), 2.35 (s, 3H), 5.64 (s, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H).

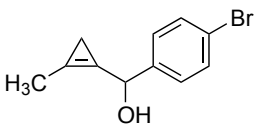
***RS*-(2-methylcycloprop-1-enyl)(4-methoxyphenyl)methanol (95c)**



From 4-methoxybenzaldehyde according to the general method in 64% yield after purification with 30% ethyl acetate: hexanes as a yellow oil. The ^{1}H NMR spectrum agreed with literature values.[38]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J* = 8.4 Hz, 1H), 1.06 (d, *J* = 8.4 Hz, 1H), 2.10 (d, *J* = 1.3 Hz, 3H), 3.81 (s, 3H), 5.62 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H).

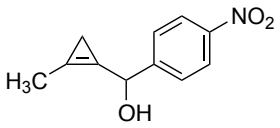
***RS*-(2-methylcycloprop-1-enyl)(4-bromophenyl)methanol (95b)**



From 4-bromobenzaldehyde according to the general method in 87% yield after purification with 20% ethyl acetate: hexanes as a yellow semi solid. The ^{1}H NMR spectrum agreed with literature values.[38]

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.01 (d, *J* = 8.4 Hz, 1H), 1.05 (d, *J* = 8.4 Hz, 1H),2.08 (d, *J* = 1.5 Hz, 3H), 5.63 (s, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H).

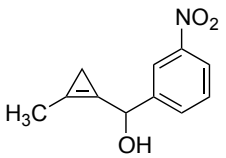
_RS_-(2-methylcycloprop-1-enyl)(4-nitrophenyl)methanol (95e)



From 4-nitrobenzaldehyde according to the general method in 94% yield after purification with 50% Et_2O:pentane to give the title compound **95e** as yellow semi-solid.

IR (thin film, cm^{-1})	3594, 3054, 2986, 1268.
^{1}H NMR (400 MHz, $CDCl_3$) δ	1.05 (d, *J* = 8.3 Hz, 1H), 1.08 (d, *J* = 8.3 Hz, 1H), 2.11 (d, *J* = 1.4 Hz, 3H), 5.80 (s, 1H), 7.61 (d, *J* = 8.9 Hz, 2H), 8.24 (d, *J* = 8.9 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ	9.1, 11.4, 69.2, 110.0, 111.6, 123.8 (2 × overlapping resonances), 127.0, 148.4
HRMS-FAB (*m/z*)	$(2M + NH_4)^+$: for $C_{22}H_{26}N_3O_6$ calc. 428.1822, found 428.1828.

_RS_-(2-methylcycloprop-1-enyl)(3-nitrophenyl)methanol (95f)

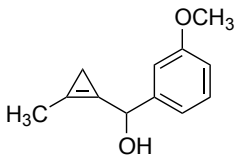


From 3-nitrobenzaldehyde according to the general method to produce the title compound **95f** in an 88% yield without further purification as an off white semi solid.

IR (thin film, cm^{-1})	3583, 2857, 1529, 1350.

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.04 (d, *J* = 8.3 Hz, 1H), 1.08 (d, *J* = 8.3 Hz, 1H), 2.11 (d, *J* = 1.4 Hz, 3H), 5.79 (s, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.81 – 7.72 (m, 1H), 8.14 - 8.18 (m, 1H), 8.29 – 8.31 (m, 1H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	9.1, 11.4, 69.1, 109.9, 111.5, 121.4, 122.8, 129.5, 132.5, 143.4, 189.9.
MS (+EI) *m/z*	228 (M +Na, 100), 206 (M +H, 3), 102 (40).
HRMS (+EI) *m/z*	for $C_{11}H_{11}NO_3Na$ calc. 228.0636, found 228.063.

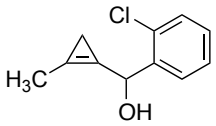
***RS*-(2-methylcycloprop-1-enyl)(3-methoxyphenyl)methanol (95g)**



From 3-methoxybenzaldehyde, following the general procedure. The title compound **95g** was isolated in a 30% yield after purification with 20% ethyl acetate: hexanes as a yellow oil.

IR (thin film, cm^{-1})	3403, 2943, 2869, 1260.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.02 (d, *J* = 8.4 Hz, 1H), 1.06 (d, *J* = 8.4 Hz, 1H), 2.09 (d, *J* = 1.2 Hz, 3H), 3.80 (s, 3H), 5.64 (bs, 1H), 6.82-6.86 (m, 1H), 6.96-6.99 (m, 2H), 7.27 (t, *J* = 8.1 Hz, 1H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	20.0, 20.9, 55.3, 112.6, 113.5, 119.9, 121.1, 128.3, 129.7, 138.1, 159.8, 162.3.
MS (+EI) *m/z*	213 (M +Na, 100), 190 (M +, 5), 173 (45).
HRMS (+EI) *m/z*	for $C_{12}H_{15}O_2$ calc. 191.1072, found 191.1067.

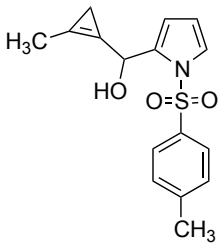
***RS*-(2-methylcycloprop-1-enyl)(2-chlorophenyl)methanol (95h)**



From 2-chlorobenzaldehyde, following the general procedure. The title compound **95h** was isolated in a >99% yield after purification with 20% ethyl acetate: hexanes as a yellow oil.

IR (thin film, cm^{-1})	3357, 2964, 2871, 1441.
^1H NMR (300 MHz, $CDCl_3$) δ	1.03 (s, 2H), 2.06 (s, 3H), 2.59 (bs, 1H), 6.03 (bs, 1H), 7.22-7.28 (m, 2H), 7.30-7.37 (m, 1H), 7.50-7.53 (m, 1H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	9.1, 11.4, 67.2, 109.7, 110.6, 127.1, 127.9, 128.9, 129.6, 132.3, 138.7.
MS (+EI) *m/z*	217 (M +Na, 20), 195 (M +H, 20), 177 (100), 142 (35).
HRMS (+EI) *m/z*	for $C_{11}H_{12}ClO$ calc. 195.0571, found 195.0569.

***RS*-2-methylcycloprop-1-enyl)[1-(p-toluenesulfonyl)pyrrol-2-yl]methanol (95i)**

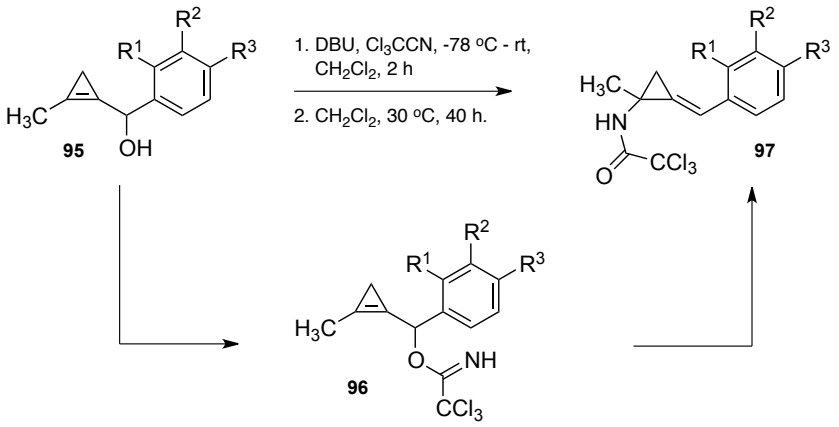


From *N*-toluenesulfonylpyrrole-2-carboxaldehyde, following the general procedure. The title compound **95i** was isolated in a 29% yield after purification in 100% CH_2Cl_2 as a yellow oil.

IR (thin film, cm^{-1})	3534, 2948, 2869, 1596, 1362, 1173.
^1H NMR (300 MHz, $CDCl_3$) δ	0.99 (d, J = 8.4 Hz, 1H), 1.05 (d, J = 8.4 Hz, 1H), 2.09 (d, J = 1.5 Hz, 3H), 2.40 (s, 3H), 2.94

	(d, *J* = 6 Hz, 1H), 5.99 (s, 1H), 6.22-6.25 (m, 2H), 7.26-7.30 (m, 3H), 7.73 (d, *J* = 8.4 Hz, 2H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	9.9, 11.5, 21.7, 62.8, 109.1, 110.8, 111.7, 114.3, 123.8, 126.9, 130.0, 134.9, 136.2, 145.2.
MS (+EI) *m/z*	326 (M +Na, 97), 304 (M+, 48), 272 (9).
HRMS (+EI) *m/z*	for $C_{16}H_{17}NO_3SNa$ calc. 326.0826, found 326.0821.

8.3 General procedure for the synthesis of benzylidenecyclopropyl trichloroacetamides

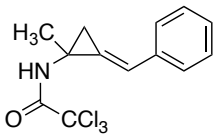


To a stirred solution of cyclopropenylcarbinol (1 equiv.) in CH_2Cl_2 (~0.1 M), was added DBU (0.15 eqiv.) followed by trichloroacetonitrile (1.5 equiv.) at -78 °C. The resulting solution was allowed to warm to -10 °C over a period of 2 h before the reaction mixture was evaporated to dryness under reduced pressure. The resulting oil was identified as the intermediate imidate, which was pure enough to use directly in the rearrangement step.

A solution of imidate (1 equiv.) and K_2CO_3 (1.5 equiv.) in CH_2Cl_2 (1 mL) were stirred at 30 °C for 40 h. After this time the solution was filtered before removal of solvent by evaporation under reduced pressure. The crude semi-solid was purified by means of flash chromatography on a neutral alumina column (ethyl acetate/hexanes) to yield the exocyclic cyclopropenyl trichloroacetamide. It should be noted that the CCl_3 carbon of the compounds were typically not identified within the ^{13}C NMR

spectra of the purified compounds. Appropriately, most compounds were reported with one carbon resonances less than what would be expected.

_RS_-1-[(_E_)-2-Phenylmethylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97a)



From **95a** according to the general method isolated in a 83% yield over two steps after purification with 20% ethyl acetate: hexanes as a off white semi solid.

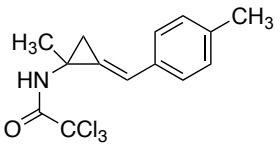
Imidate:

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.07 (d, *J* = 8.4 Hz, 1H), 1.15 (d, *J* = 8.4 Hz, 1H), 2.09 (d, *J* = 1.4 Hz, 3H), 6.82 (s, 1H), 7.32-7.40 (m, 3H), 7.45-7.48 (m, 2H), 8.42 (s, 1H).

Amide:

IR (thin film, cm^{-1})	3415, 3054, 2986, 1719, 1492, 1421, 1265, 895.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.61 (s, 3H), 1.80 (dd, *J* = 10.8, 2.6 Hz, 1H), 1.86 (dd, *J* = 10.8, 2.6 Hz, 1H), 7.06 (bs, 1H), 7.19 (t, *J* = 2.6 Hz, 1H), 7.27-7.38 (m, 3H), 7.45-7.56 (m, 2H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	20.0, 21.0, 29.9, 121.2, 127.2, 127.9, 128.0, 128.7, 136.6, 162.3.
HRMS-FAB *m/z*	for $C_{13}H_{12}NOCl_3$ +H calc. 304.0062, found 304.0057.

_RS_-1-[(_E_)-2-(4-Methylphenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97d)



From **95d** according to the general method isolated in a 98% yield over two steps after purification with 30% ethyl acetate: hexanes as a off white semi solid.

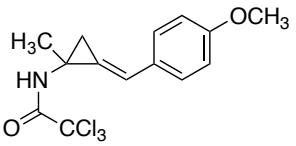
Imidate:

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.06 (d, *J* = 8.4 Hz, 1H), 1.14 (d, *J* = 8.4 Hz, 1H), 2.10 (d, *J* = 1.5 Hz, 3H), 2.36 (s, 3H), 6.78 (s, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 8.39 (s, 1H).

Amide:

IR (thin film, cm^{-1})	3417, 3050, 3030, 2971, 2929, 2864, 1715, 1513, 1489, 1236, 821, 711.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.60 (s, 3H), 1.77 (dd, *J* = 10.6, 2.6 Hz, 1H), 1.83 (dd, *J* = 10.7, 2.6 Hz, 1H), 2.35 (s, 3H), 7.01 (bs, 1H), 7.11-7.19 (m, 3H), 7.44 (d, *J* = 8.1 Hz, 2H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	20.1, 23.1, 21.5, 30.0, 121.1, 126.9, 127.2, 129.5, 134.0, 138.0, 162.4.
HRMS-FAB *m/z*	for $C_{14}H_{15}NOCl_3$ calc. 318.0221, found 318.0214.

_RS_-1-[(_E_)-2-(4-Methoxyphenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97c)



From **95c** according to the general method isolated in a 77% yield over two steps after purification with 30% ethyl acetate: hexanes as a off white semi solid.

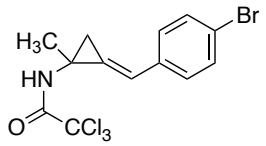
Imidate:

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.09 (dd, *J* = 23.7, 8.4 Hz, 2H), 2.09 (d, *J* = 1.5 Hz, 3H), 3.79 (s, 3H), 6.75 (s, 1H), 6.85-6.92 (m, 2H), 7.38 (d, *J* = 8.7, 2H), 8.38 (s, 1H).

Amide:

IR (thin film, cm^{-1})	3423, 3054, 2986, 1717, 1512, 1421, 1265, 705.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.60 (s, 3H), 1.75 (dd, *J* = 8.6, 2.4 Hz, 1H), 1.81 (dd, *J* = 10.7, 2.8 Hz, 1H), 3.81 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H).
^{13}C NMR (70 MHz, $CHCl_3$) δ	19.8, 21.0, 29.9, 55.3, 114.1, 120.5, 125.5, 128.4, 129.4, 159.4, 162.3.
HRMS (+EI) *m/z*	for $C_{14}H_{15}NO_2Cl_3$ calc. 334.0170, found 334.0157.

_RS_-1-[(_E_)-2-(4-Bromophenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97b)



From **95b** according to the general method isolated in a 63% yield over two steps after purification with 20% ethyl acetate: hexanes as a off white semi solid.

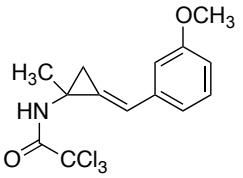
Imidate:

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.06 (d, *J* = 8.3 Hz, 1H), 1.14 (d, *J* = 8.3 Hz, 1H), 2.09 (d, *J* = 1.5 Hz, 3H), 6.76 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 8.43 (s, 1H).

Amide:

IR (thin film, cm^{-1})	3289, 2922, 2850, 1694, 1506.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.60 (s, 3H), 1.76 (dd, *J* = 10.9, 2.6 Hz, 1H), 1.83 (dd, *J* = 10.9, 2.6 Hz, 1H), 7.07 (s, 1H), 7.13 (t, *J* = 2.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H).
^{13}C NMR (70 MHz, $CHCl_3$) δ	19.9, 20.9, 29.9, 120.3, 121.8, 128.7, 128.8, 131.8, 135.6, 162.3.
MS (+EI) *m/z*	405 (M +Na, 100), 301 (28).
HRMS (+EI) *m/z*	for $C_{13}H_{11}BrCl_3NO$ +Na calc. 403.8987, found 403.8982.

_RS_-1-[(_E_)-2-(3-Methoxyphenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97g)



From **95g** according to the general method isolated in a 47% yield over two steps after purification with 20% ethyl acetate: hexanes as a colourless oil.

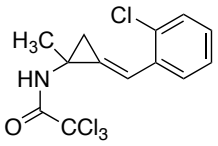
Imidate:

Not identifiable in ^{1}H NMR of crude mixture.

Amide:

IR (thin film, cm^{-1})	3443, 2957, 1600, 1511, 1249, 1170, 1030.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.60 (s, 3H), 1.79 (dd, *J* = 10.9, 2.6 Hz, 1H), 1.86 (dd, *J* = 10.9, 2.6 Hz, 1H), 3.82 (s, 3H), 6.81-6.86 (m, 1H), 7.06 (s, 1H), 7.09 (t, *J* = 2.4 Hz, 1H), 7.12 (ap, 1H), 7.15-7.16 (m, 1H), 7.27 (t, *J* = 7.8 Hz, 1H).
^{13}C NMR (70 MHz, $CDCl_3$) δ	20.0, 20.9, 29.9, 55.3, 92.6, 112.6, 113.5, 119.9, 121.1, 128.3, 129.7, 138.1, 159.8, 162.3.
MS (+EI) *m/z*	356 (M+Na, 100), 213 (17).
HRMS (+EI) *m/z*	for $C_{14}H_{14}Cl_3NO_2$ +Na calc. 355.9987, found 355.9982.

_RS_-1-[(_E_)-2-(2-Chlorophenyl)methylidene-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97h)



From **95h** according to the general method isolated in a 48% yield over two steps after purification with 20% ethyl acetate: hexanes as a off white semi solid.

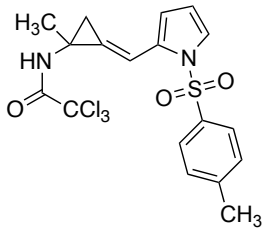
Imidate:

^{1}H NMR (300 MHz, $CDCl_3$) δ	1.08 (d, *J* = 8.4 Hz, 1H), 1.26 (d, *J* = 8.4 Hz, 1H), 2.08 (d, *J* = 1.5 Hz, 3H), 7.15 (s, 1H), 7.25-7.32 (m, 2H), 7.38-7.41 (m, 1H), 7.53-7.56 (m, 2H), 8.46 (s, 1H).

Amide:

IR (thin film, cm^{-1})	3317, 2968, 1695, 1495.
^{1}H NMR (300 MHz, $CDCl_3$) δ	1.62 (s, 3H), 1.81 (dd, *J* = 11.1, 2.6 Hz, 1H), 1.88 (dd, *J* = 11.1, 2.6 Hz, 1H), 7.10 (bs, 1H), 7.18-7.25 (m, 2H), 7.38 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.58 (t, *J* = 2.6 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.8 Hz, 1H).
^{13}C NMR (70 MHz, $CHCl_3$) δ	20.1, 20.9, 30.0, 117.1, 126.8, 127.2, 129.0, 129.9, 130.7, 133.6, 134.2, 162.2.
MS (+EI) *m/z*	359 (M +Na, 47), 336 (M, 22).
HRMS (+EI) *m/z*	for $C_{13}H_{11}Cl_4NO$ +Na calc. 359.9492, found 359.9487.

***RS*-1-[(*E*)-2-{[1-(*p*-Tolylsulfonyl)-1*H*-pyrrol-2-yl]methylidene}-1-methylcyclopropylamino]-2,2,2-trichloro-1-ethanone (97i)**



From **95i** according to the general method isolated in a <99% yield over two steps after purification with 100% CH_2Cl_2 as a yellow oil.

Imidate:

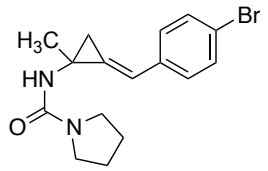
Rearrangement was too rapid to characterise intermediate imidate.

Amide:

IR (thin film, cm^{-1})	3364, 2969, 2027, 1713, 1494, 1367, 1174.
^1H NMR (300 MHz, $CDCl_3$) δ	1.55 (s, 3H), 1.55-1.59 (m, 1H), 1.62 (dd, *J* = 11.1, 2.7 Hz, 1H), 2.36 (s, 3H), 6.27 (t, *J* = 3.9 Hz, 1H), 6.52-6.52 (m, 1H), 6.99 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.64 (t, *J* = 2.7 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H).
^{13}C NMR (70 MHz, $CHCl_3$) δ	19.6, 21.0, 21.7, 31.4, 110.5, 112.5, 112.7, 123.1, 127.1, 128.5, 130.1, 131.9, 135.9, 145.1, 161.98.
MS (+EI) *m/z*	447 (M+H, 10), 318 (100), 264 (99).
HRMS (+EI) *m/z*	for $C_{18}H_{17}Cl_3N_2O_3S$ +H calc. 447.0103, found 447.0098.

8.4 Manipulation of benzylidenecyclopropyl trichloroacetamides

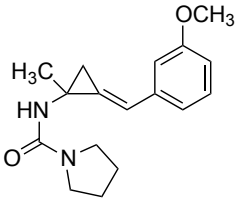
_RS_-1-{(_E_)-2-[(4-Bromophenyl)methylidene]-1-methylcyclopropylamino}(1-pyrrolidinyl)formaldehyde (106b)



To a solution of **97b** (62 mg, 0.16 mmol) in anhydrous DMF (2 mL) under nitrogen was added Cs_2CO_3 (140 mg, 0.43 mmol) at −78 °C. The mixture was stirred for 1 h before the slow addition of pyrrolidine (140 μL, 120 mg, 1.69 mmol), which was subsequently allowed to warm to room temperature over 18 h. After this time the mixture was diluted with 50% ethyl acetate in hexanes and washed with water. The crude mixture was dried on Na_2SO_4, filtered and had the solvent removed under reduced pressure. The crude oil was purified by means of flash chromatography with 100% ethyl aceate to afford **106b** as a yellow oil in a 39% yield (21.0 mg, 0.06 mmol).

IR (thin film, cm^{-1})	3252, 2970, 1689, 1489, 1383, 1161.
^1H NMR (400 MHz, $CDCl_3$) δ	1.56 (s, 3H), 1.74-1.77 (m, 4H), 2.02 (s, 3H), 2.41-2.47 (m, 2H), 2.68-2.72 (m, 2H), 6.65 (bs, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H).
^{13}CNMR (100 MHz, $CDCl_3$) δ	11.8, 23.9, 24.5, 46.2, 77.9, 122.1, 129.7, 130.3, 131.0, 131.5, 158.5, 171.7.
MS (+EI) *m/z*	357 (M +Na, 37), 335 (M +H, 72), 268 (100), 175 (67).
HRMS (+EI) *m/z*	For $C_{16}H_{19}BrNO_2$ +H calc. 335.0759, found 335.0754.

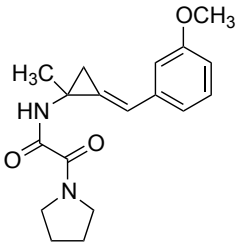
***RS*-1-{(*E*)-2-[(3-Methoxyphenyl)methylidene]-1-methylcyclopropylamino}(1-pyrrolidinyl)formaldehyde (106g)**



To a solution of **97g** (88.1 mg, 0.26 mmol) in anhydrous DMF (2 mL) under nitrogen was added Cs_2CO_3 (214.5 mg, 0.75 mmol) at −78 °C. The mixture was allowed to stir for 1 h before the slow addition of pyrrolidine (130 μL, 112 mg, 1.57 mmol), which was subsequently allowed to warm to room temperature over 18 h. After this time the mixture was diluted with 50% ethyl acetate in hexanes and washed with water. The crude mixture was dried on Na_2SO_4, filtered and had the solvent removed under reduced pressure. The crude oil was purified by means of flash chromatography with 30% ethyl aceate: hexanes to afford **106g** as a yellow oil in a 24% yield (18.3 mg, 0.06 mmol).

IR (thin film, cm^{-1})	3222, 2964, 2834, 1689, 1600, 1578.
^1H NMR (400 MHz, $CDCl_3$) δ	1.57 (s, 3H), 1.75-1.78 (m, 4H), 2.03 (s, 3H), 2.42-2.47 (m, 2H), 2.69-2.74 (m, 2H), 3.82 (s, 3H), 6.54 (bs, 1H), 6.86-6.89 (m, 1H), 7.01-7.03 (m, 2H), 7.32 (t, J = 8.4 Hz, 1H).
^{13}CNMR (100 MHz, $CDCl_3$) δ	11.8, 23.9, 24.5, 46.7, 55.3, 77.7, 113.7, 114.9, 121.8, 129.3, 130.7, 132.7, 158.2, 159.5, 172.1.
MS (+EI) *m/z*	287 (M +H, 100), 216 (7), 72 (45).
HRMS (+EI) *m/z*	For $C_{17}H_{22}N_2O_2$ +H calc. 287.1759, found 287.1754.

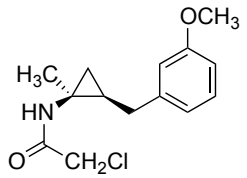
***RS*-1-{(*E*)-2-[(*m*-methoxyphenyl)methylidene]-1-methylcyclopropylamino}-2-(1-pyrrolidinyl)-1,2-ethanedione (107)**



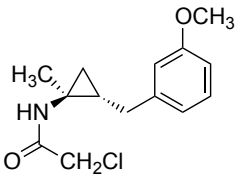
To a solution of **97g** (19.8 mg, 0.06 mmol) in DMF (1 mL, bench grade) under nitrogen was added pyrroldine (50 μL, 43 mg, 0.6 mmol) followed by Cs_2CO_3 (45.0 mg, 0.14 mmol) at −78 °C. The mixture was subsequently allowed to warm to room temperature over 18 h. After this time the mixture was diluted with 50% ethyl acetate in hexanes (5 mL) and washed with water (5 x 5 mL). The crude mixture was dried on Na_2SO_4, filtered and had the solvent removed under reduced pressure. The crude oil was purified by means of flash chromatography with 30% ethyl aceate: hexanes to afford **107** as a yellow oil in 58% yield (10.8mg, 0.03 mmol).

IR (thin film, cm^{-1})	3297, 2969, 1687, 1623, 1428.
^1H NMR (400 MHz, $CDCl_3$) δ	1.56 (s, 3H), 1.76 (dq, *J* = 10.8, 2.8 Hz, 2H), 1.83 (p, *J* = 6.6 Hz, 2H), 1.95 (p, *J* = 6.6 Hz, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 4.00 (dt, *J* = 6.8, 3.6 Hz, 2H), 6.79-6.82 (m, 1H), 7.07-7.12 (m, 3H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.9 (bs, 1H).
^{13}CNMR (100 MHz, $CDCl_3$) δ	19.9, 21.5, 23.5, 26.9, 28.5, 48.0, 48.8, 55.3, 112.4, 113.3, 119.9, 120.4, 129.6, 129.7, 138.6, 159.3, 159.9, 161.4.
MS (+EI) *m/z*	337 (M +Na, 100).
HRMS (+EI) *m/z*	For $C_{18}H_{22}O_3N_2$ +Na calc. 337.1528, found 337.1523.

_RS_-2-chloro-1-{2-[(_m_-methoxyphenyl)methyl]-1-methylcyclopropylamino}-1-ethanone (113a & 113b)



major



minor

Under an atmosphere of H_2, **97g** (88.9 mg, 0.26 mmol) was stirred in ethanol (10 mL) for 2 days with Pd/C (8.0 mg) at room temperature. After this time the mixture was passed through a short plug of celite before the solvent was removed under reduced pressure to reveal a brown oil which was subsequently purified be means of flash chromatography with 30% ethyl acetate: hexanes to reveal the mixture of **113a** and **113b** as a slightly yellow oil in a 41% yield (30.3 mg, 0.11 mmol).

IR (thin film, cm^{-1})	3292, 3096, 2959, 1663, 1489, 1251.
^1H NMR (400 MHz, $CDCl_3$) δ	0.57 (t, *J* = 6.0 Hz *minor isomer*), 0.68 (t, *J* = 6.0 Hz *major isomer*), 1.01 (dd, *J* = 9.0, 6.0 Hz, 1H, *major isomer*), 1.05 (dd, *J* = 10.0, 6.0 Hz, 1H, *minor isomer*), 1.20-1.28 (m, 1H, *major isomer*), 1.28-1.34 (m, 1H, *major isomer*), 1.44 (s, 3H, *major isomer*), 1.49 (s, 3H, *minor isomer*), 2.51 (dd, *J* = 15.0, 8.0 Hz, 1H, *minor isomer*), 2.62 (dd, *J* = 15.0, 8.0 Hz, 1H, *major isomer*), 2.83 (dd, *J* = 15.0, 7.0 Hz, 1H, *major isomer*), 2.93 (dd, *J* = 15.0, 6.0 Hz, 1H, *minor isomer*), 3.83 (s, 3H, *major isomer*), 3.83 (s, 3H, *minor isomer*), 3.99 (s, 2H, *minor isomer*), 4.03 (s, 2H, *major isomer*), 6.78-6.90 (m, 3H, *minor and major isomer*), 7.25 (t, *J* = 8.0 Hz, 1H, *major isomer*), 7.25 (t, *J* = 8.0 Hz, 1H, *major isomer*).

^{13}C NMR (100 MHz, $CDCl_3$) δ	18.3, 20.4, 20.6, 23.6, 25.4, 26.2, 33.3, 33.5, 35.0, 35.3, 42.8, 42.9, 55.3, 55.3, 111.4, 111.5, 114.1, 114.3, 120.6, 120.8, 129.5, 129.7, 142.7, 142.9, 159.8, 159.9, 166.0, 166.8.
MS (+EI) *m/z*	290 (M +Na, 10), 285 (M +NH_4, 100), 268 (M +H, 95).
HRMS (+EI) *m/z*	For $C_{14}H_{18}ClNO_2$ +Na calc. 290.0923, found 290.0918.

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